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Research Article

Posaconazole-Loaded PVA/SA-L-Valine Composite for Sustained Drug Delivery with Docking Study

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Received: 14 April 2026; **Revised:** 24 April 2026; **Accepted:** 7 May 2026

Abstract: Self-Assembled L-valine (SA-L-valine) was synthesized and Posaconazole (POS)-Loaded Polyvinyl Alcohol (PVA) with SA-L-valine composite films were fabricated using a solvent evaporation method. The prepared samples were characterized by Fourier-Transform Infrared Spectroscopy (FT-IR), X-Ray Diffraction (XRD), and Field-Emission Scanning Electron Microscopy (FE-SEM). XRD results confirmed that SA-L-valine was properly incorporated into the POS/PVA matrix, forming an ordered morphology. FT-IR spectra revealed strong intermolecular interactions, suggesting effective complex formation, and FE-SEM images showed a clear sheet-like surface morphology with uniform structural organization. The drug release study at pH 3.4, 5.5, and 7.4 showed cumulative releases of 96.01%, 98.23%, and 95.52% within 24 h, respectively. The highest release at pH 5.5, which corresponds to the natural skin surface pH, indicates that the PVA/SA-L-valine film loaded with posaconazole is suitable for topical antifungal applications. In vitro antifungal activity evaluation using the disk diffusion method demonstrated significant inhibitory effects against fungal pathogens. Furthermore, molecular docking studies with the lipid transfer protein Sec14p from *Saccharomyces cerevisiae* demonstrated favorable binding interactions, confirming that the drug maintained its biological activity after formulation. These findings suggest that this composite may be a promising sustained-release antifungal drug delivery system.

***Keywords*:** drug release, docking study, L-valine, posaconazole, self-assembly

1. Introduction

Fungal infections are a serious problem in many countries, including developed countries, and candidiasis is the most common fungal infection. Candida species are opportunistic fungi that can thrive in the human flora of the digestive tract, vagina, or skin, and most people do not experience any symptoms due to their presence. When the immune system is weakened, Candida can cause both skin and systemic infections. Treatment of candidiasis is a long-term and challenging process affected by increasing fungal resistance. Current efforts are focused on discovering new compounds, new drug combinations, and new drug delivery systems that will enable effective and safe treatment.[1]

Polyvinyl Alcohol (PVA) is a polymer that can be synthesized and is water-soluble, but when cross-linked using chemical or physical methods, it can form an insoluble hydrogel matrix. The use of PVA is advantageous because it is biocompatible, non-toxic, transparent, and biodegradable.[2-6] In the present-day scenario, PVA

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hydrogels are being researched with or without additional polymer composites and polymeric nanoparticles by loading different drug categories and evaluating their efficacy in treating different infections. PVA-based hydrogels have gained widespread recognition because they can be tailored to meet the required stability, swelling index, and drug release pattern.[7-10]

The purpose of wound dressings is to promote re-epithelialization, protect against wound infection, guard against skin dryness, and avoid further skin damage. The way wounds were managed was greatly altered by the introduction of semipermeable films, which was one of the earliest significant developments in wound care. Sterile polyurethane plastic sheets coated with non-allergenic acrylic adhesive are used as a transparent main wound cover for the majority of their use. A moist wound environment is maintained by transparent film bandages, allowing for gas exchange and preventing contamination from external germs.[11] The passage of air and water vapor is possible, but liquids and microorganisms are prohibited. The ability of valine to control the production and function of antimicrobial components and barriers in mammary glands has been reported. The mammary glands absorb approximately 40% of the amino acids, and valine is one of them, a branched-chain amino acid.[12] Valine promotes the production of β-casein and α-lactalbumin in cultured porcine Mammary Epithelial Cells (MECs).[13] β-casein is an abundant protein in milk, and α-lactalbumin is an enzyme involved in the synthesis of lactose. Cultured porcine MECs also experience a boost in milk fat production due to valine. In addition, branched-chain amino acids have been reported to modulate intestinal mucosal immunity and barrier function in pigs.[14] Furthermore, valine supplementation has been demonstrated to enhance intestinal barrier function by modulating protein messenger Ribonucleic Acid (mRNA) expression in fish.[15]

Posaconazole (POS) is a second-generation triazole derivative that is safe and well-tolerated, and is used to prevent and treat invasive fungal infections. The inhibition of lanosterol 14α-demethylase enzyme, which is involved in ergosterol synthesis and causes cell membrane instability, is what makes POS so powerful against fungal infections. The application of POS has been shown to be helpful for the treatment of Candida, Aspergillus, Fusarium, and Zygomycetes. POS is included in the second group of the Biopharmaceutics Classification System (BCS) because it has high permeability but limited solubility. The absorption of POS depends on several factors, such as the pH of the environment, the food eaten, and other medications, as well as the strength and quantity of POS doses.[16]

Molecular docking is a fast and efficient computational method that can predict bioactive compounds for a given protein and inversely predict the target protein of a single bioactive compound. Conducting molecular docking studies to identify potential targets and predict probable targets of title compounds from antifungal drug proteins can be guided by the antifungal activities of benzoxazole and benzothiazole derivatives.[17]

Traditional drug delivery systems often suffer from limitations such as burst release, poor drug stability, low bioavailability, and a lack of controlled behavior or stimuli responsiveness. These drawbacks can reduce therapeutic efficacy and cause side effects due to uncontrolled drug diffusion. In contrast, this study presents a POS/PVA/SA-L-valine-based film system designed to achieve controlled pH-responsive drug release. The incorporation of self-assembled L-valine structures within the polymer matrix enhances structural stability and modulates the drug diffusion behavior. This strategy offers improved release control, increased efficiency, and enhanced suitability for topical drug delivery compared to traditional drug delivery approaches. We used posaconazole as a model antifungal drug[18] and focused on the drug loading and controlled release behavior in PVA/SA-L-valine films. Physicochemical properties were evaluated by Fourier-Transform Infrared Spectroscopy (FT-IR), X-Ray Diffraction (XRD), and Field-Emission Scanning Electron Microscopy (FE-SEM) analysis. Drug release was assessed by Ultraviolet-Visible (UV-Vis) spectroscopy, and antifungal activity was evaluated by disk diffusion. The mechanism of antifungal action was further supported by molecular docking studies using Sec14p from *Saccharomyces cerevisiae*.

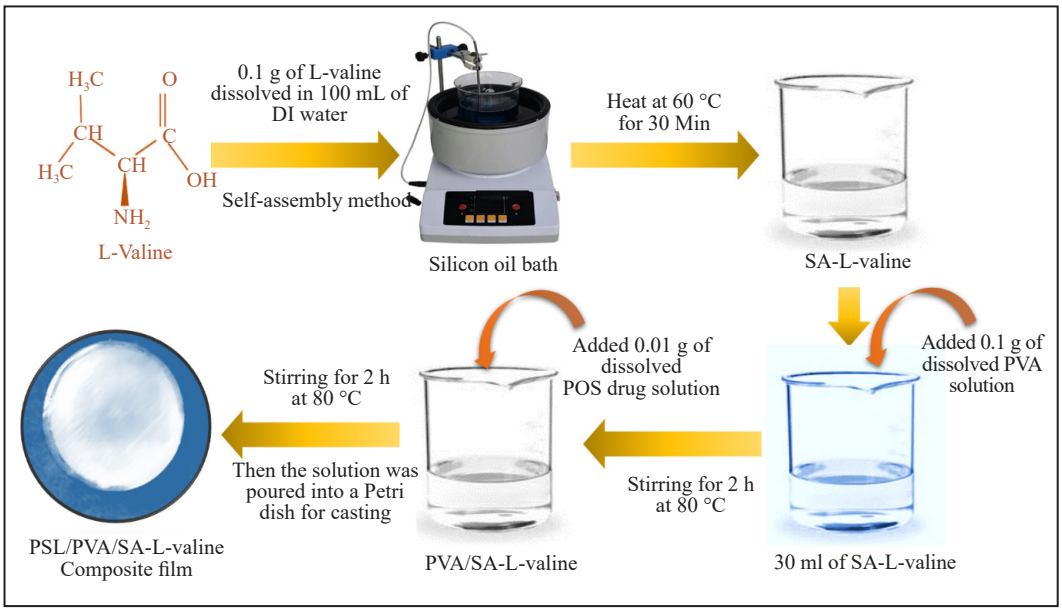
2. Experimental methods

2.1 *Materials*

Analytical grade was used for all the chemicals. All glassware was washed with acetone, rinsed with deionized water, and dried in a hot air oven at 100 °C. L-valine was used for the synthesis of self-assembly. The powder of Posaconazole was obtained from Sigma Aldrich. PVA (72,000 g/mol) was obtained from OTTO Chemicals. Phosphate-Buffered Saline (PBS) solution was used to study the potential of drug delivery.

2.2 *Synthesis of SA-L-valine*

100 mL of double-distilled water was used to dissolve about 0.1 g of AR L-valine. The heating process in a silicone oil bath involved the use of a magnetic stirrer and a hot plate to maintain a temperature of 60 °C for 30 minutes. It was allowed to cool down gradually to room temperature (Scheme 1) before becoming self-assembled.



Scheme 1. Synthesis scheme of POS/PVA/SA-L-valine composite film

2.3 *Synthesis of posaconazole drug-loaded PVA-SA-L-valine composite film*

About 0.1 g of dissolved PVA was added to 30 mL of self-assembled L-valine, and it was subjected to magnetic stirring for 2 h at 80 °C. Then, 0.01 g of posaconazole drug was dissolved in 50 mL of PBS solution at a maintained pH-3.4. Then the drug solution was added to the SA-L-valine + PVA solution, followed by continuous stirring for 2 h. Then, it was poured into a petri dish for film casting. The film obtained was utilized in drug delivery and kinetic measurement (Scheme 1).

2.4 *Characterisation studies*

The Cu-Kα radiation (λ = 1.5418 Å) from an X-ray diffractometer (XPERT PRO, Malvern Panalytical) was utilized to analyze the sample diffraction profiles. The materials' functional groups were assigned using an FT-IR spectrophotometer (IR Tracer-100 Shimadzu). A Shimadzu UV-2600 was used to detect Diffuse Reflectance Spectra (UV-Vis DRS) between 200 and 800 nm. A CARL ZEISS-SIGMA 300 FE-SEM apparatus model was used for morphological studies.

2.5 *In vitro drug release studies*

The spectrophotometer UV-2600 from Shimadzu used absorption analysis to determine the POS content in the aliquots. The calibration curve was initially determined by preparing standard solutions. The drug-loaded film was kept suspended in glass vessels that contained PBS (pH 3.4, 5.5, and 7.4) solution at 36 °C after being loaded. The solutions were taken out at the appropriate intervals, and the POS that was released from the samples was assessed using UV absorption measurements at 255 nm.

2.6 *Molecular docking studies*

From the Brookhaven Protein Data Bank, the crystal structure of *Saccharomyces cerevisiae*'s lipid transfer protein sec14p (PDB 6F0E) was obtained. The use of AutoDock 4.2 software from The Scripps Research Institute in California (CA, USA) resulted in docking trials. Essential docking was prepared using AutoDock Tools. The docking calculations were done using a docking server (http://www.dockingserver.com). The Docking server and the MMFF94 force field were used to optimize the molecular structure of the ligand. Partial charges were added to the ligand atoms by the Gasteiger method. Non-polar hydrogen atoms were combined, and rotatable bonds were defined. A suitable protein model was used to perform docking computations. The use of Auto Dock tools resulted in the introduction of the solvation parameter, Kollman unified atom type charges, and essential hydrogen atoms. The Auto grid tool was used to create affinity (grid) maps with a 0.375 Å spacing and 60 × 60 × 60 Å grid points. The Auto Dock parameter set and distance-dependent dielectric functions were utilized to calculate van der Waals and electrostatic components. Docking simulations were conducted using the Lamarckian Genetic Algorithm (LGA) and the Solis and Wets local search method. The ligand molecules had their initial orientation, torsion, and location determined randomly. During docking, all rotatable torsions were released. During every docking experiment, there were ten distinct runs that were supposed to end with a maximum of 250,000 energy evaluations. Throughout the search, a translation step of 0.2 Å and five quaternion and torsion steps were utilized.

3. Results and discussions

3.1 *UV-Vis spectroscopy*

Figure 1 displays the UV-Vis spectrum of SA-L-valine and POS-PVA-SA-L-valine. The solution has an optical transmission of 80 percent in the UV-Vis region when monitored from longer to shorter wavelengths and has optical absorption below 300 nm. The decrease in absorption intensity is caused by the self-assembly peak of L-valine at around 250 nm. The lower cutoff wavelength of the UV region is affected by the combination of POS-PVA and SA-L-valine. The POS drug molecule interacts with PVA-SA-L-valine, reducing their susceptibility to UV absorption. The interaction could cause a masking effect, in which the carrier molecules decrease the drug's ability to absorb UV radiation.

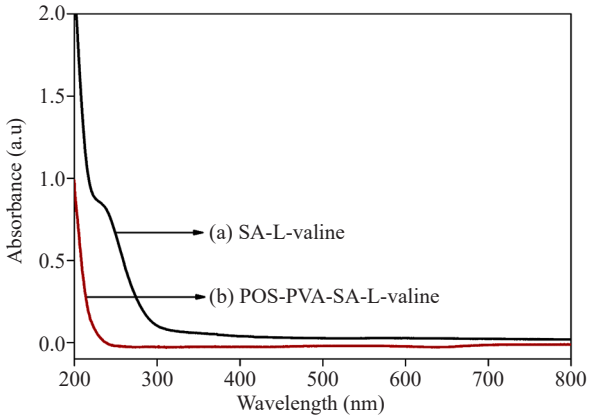


Figure 1. UV absorbance spectra of (a) SA-L-valine and (b) POS/PVA/SA-L-valine composite

3.2 *FT-IR spectroscopy*

Infrared spectra of SA-L-valine and POS-PVA-SA-L-valine can be seen in Figure 2a, b. The IR spectrum of POS-PVA-SA-L-valine is mostly caused by the internal vibrations of functional groups like NH_3, CH, and COOH. The absorption bands of POS-PVA-SA-L-valine and SA-L-valine alone were compared. A broad peak was observed at

2,954 cm^{-1} due to the symmetric stretching of methylene and N-H···O methylene. At 2,624 cm^{-1}, a combined N-H···O valence stretch was observed. The steep peaks at 1,586 cm^{-1} and 1,395 cm^{-1} are caused by the COO^- asymmetric vibration. The protonated amino group NH_3 of valine is responsible for the deformation bands observed at 1,505 cm^{-1}. At 1,270 and 1,133 cm^{-1}, the C-C stretching modes are visible. At 1,033 cm^{-1}, there is a sharp peak that is caused by the C-C-N stretching mode. At 900 cm^{-1}, the C-C=O deformation is observed. Some amino acids that were reported exhibit wavenumbers in good agreement with the proposed assignments.[19] Figure 2b shows a broad spectral peak at 3,094-3,590 cm^{-1}, which corresponds to the OH stretching vibration of the PVA hydroxyl group.[20] The C-C stretching vibrations are observed at 1,289 cm^{-1} and 1,133 cm^{-1}. From the FTIR analysis, it was observed that POS was stable in the POS-PVA-SA-L-valine blend.

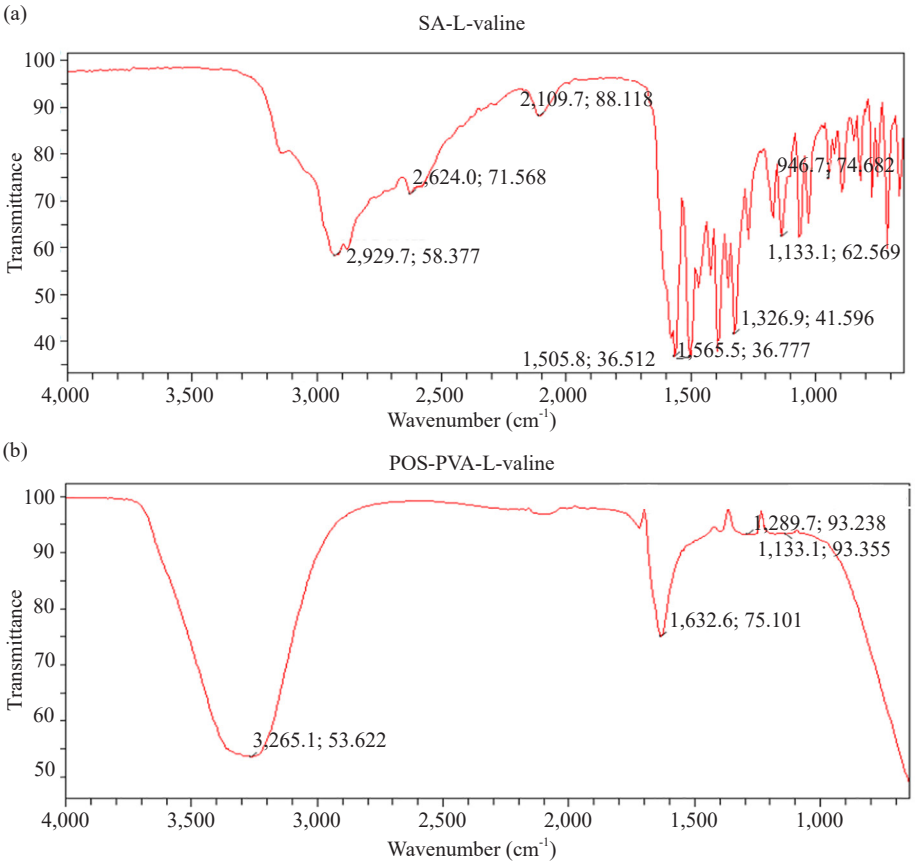


Figure 2. Infrared spectra of (a) SA-L-valine and (b) POS/PVA/SA-L-valine

3.3 *Powder XRD analysis*

The XRD study is shown in Figure 3. XRD patterns are used to analyse the crystallinity of the material. The strong peaks are found at 2θ = 15.77, 19.42, 22.23, 24.06, 29.55, 35.53, and 36.01. The crystalline nature of the SA-L-valine is revealed by the powder X-ray diffraction analysis. The experimental values along with the "hkl" indices of the corresponding reflecting planes for the SA-L-valine are well-matched with the literature reported.[21] The POS and PVA XRD peaks can be too faint to see against the background noise if it is present in the composite material in low concentrations. The drug and polymer are amorphous or semi-crystalline in structure, which prevents them from producing distinguishable peaks in XRD. Rather, they may cause a wide hump in the diffraction pattern, which would obscure their reflection peaks.

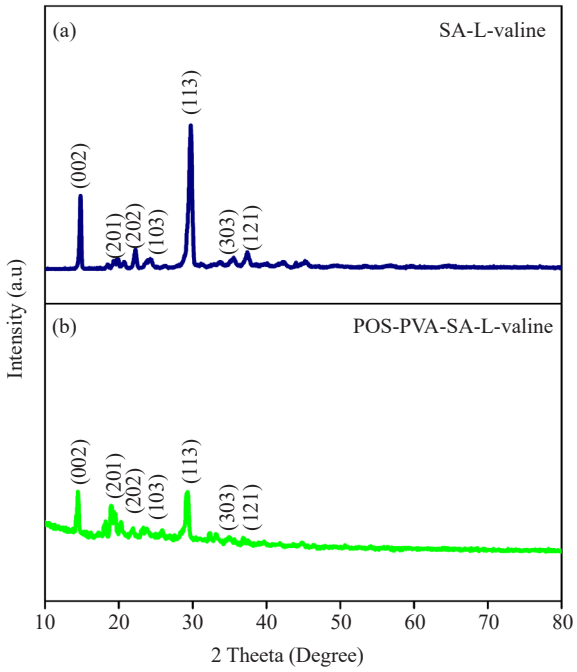


Figure 3. XRD pattern of (a) SA-L-valine and (b) POS/PVA/SA-L-valine

3.4 *FE-SEM analysis*

Figure 4a shows the FE-SEM image of SA-L-valine which demonstrates the formation of a long-range sheet-like morphology. The images reveal that the sheet-like structures in Figure 4a (100 µm scale bar) have lateral dimensions in the range of 20-80 µm. In Figure 4b (scale bar 200 µm), the assembled sheet-like aggregates exhibit larger dimensions ranging from 50 to 150 µm, confirming the formation of an extended sheet-like hydrogel network structure. Thus, an in-depth analysis of the structure-morphological relationship under varying conditions shows that the modulated L-Valine self-assembled architectures form long sheet-like structures.

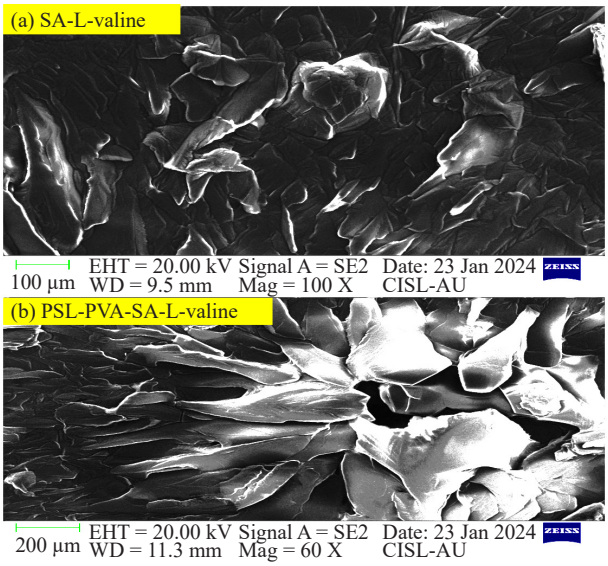


Figure 4. FE-SEM image of (a) SA-L-valine and (b) POS/PVA/SA-L-valine

3.5 *In vitro drug release*

By utilizing absorption studies with a 100 µg/mL drug solution, the λ max of posaconazole was found to be 255 nm. The absorbance of the solution at 10 µg/mL was determined in Figure 5. It was found that there was a linear correlation with R^2 = 0.992. The resulting POS/PVA/SA-L-valine films were loaded with 10 mg of posaconazole during the film casting process. The drug solution was homogeneously mixed with the polymer matrix under continuous stirring to ensure uniform distribution. The resulting drug-loaded films were dried and used for in vitro drug release and kinetic studies. The release behavior discussed below corresponds to this 10 mg drug-loaded formulation.

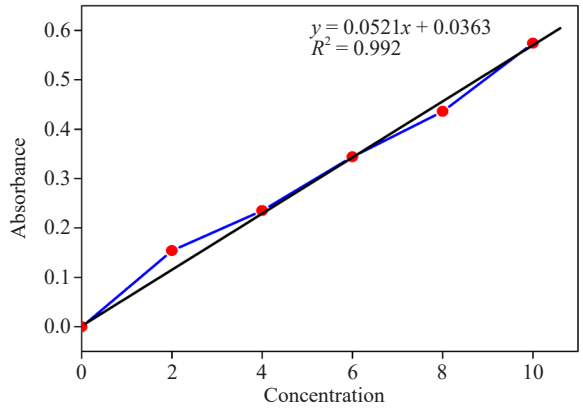


Figure 5. Calibration curve for posaconazole drug

PBS (at pH 5.5, 3.4, and 7.4) was used to study in vitro drug release, and UV-Vis spectral absorbance values were used to quantify the release of the loaded drug. The release (%) of posaconazole vs. immersion time from the film is displayed in Figure 6. In comparison to the abrupt release that occurred, it was noted that the lower slope of the release curves indicated a gradual release during the observed hours. This observation might be explained by the fact that PVA dissolves in an acidic environment when the pH is less than 5.5, 3.4, and 7.4. Additionally, it has been proposed that when the drug is evenly distributed throughout the polymeric PVA matrix, the medication may be released through a combination of mechanisms, including the diffusion of the compound through gaps and pores, swelling caused by water absorption into the matrix, and polymer erosion.

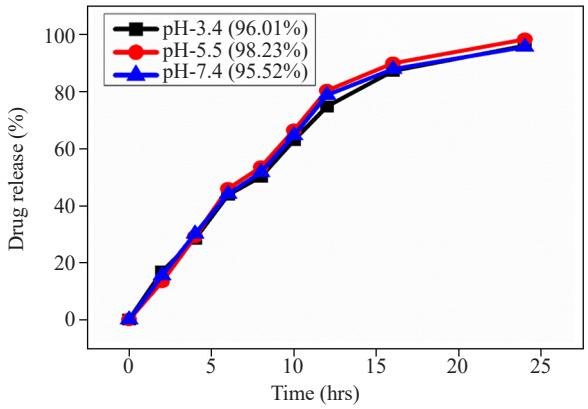


Figure 6. Drug release % of POS/PVA/SA-L-valine

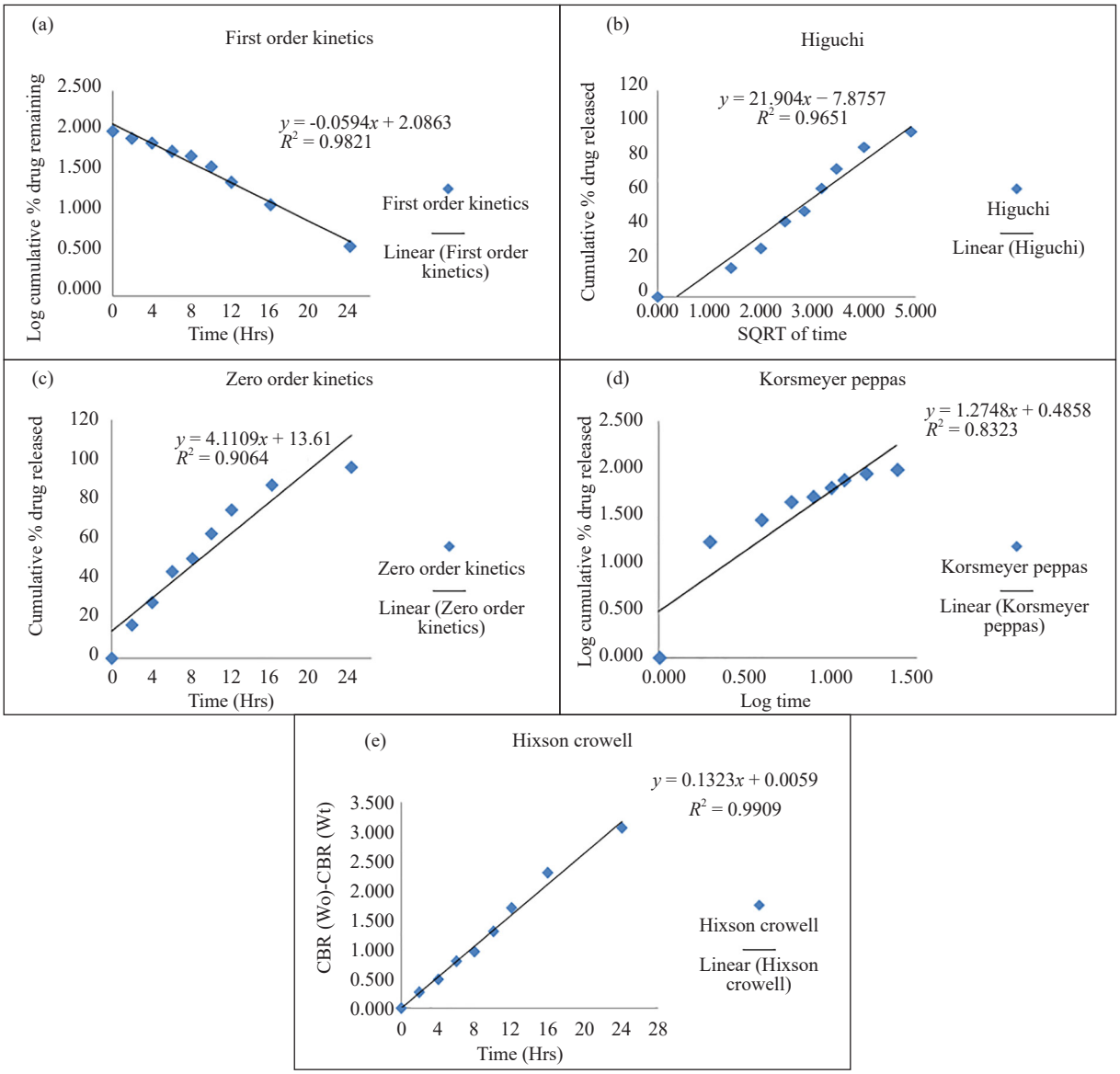


Figure 7. The Drug releases different kinetic models of POS/PVA/SA-L-valine at pH 5.5 (a) First order kinetics, (b) Higuchi, (c) Zero order kinetics, (d) Korsmeyer peppas and (e) Hixson crowell models

The release kinetics of the POS/PVA/SA-L-valine film were evaluated using different kinetic models. Several kinetic models for in vitro dissolution were fitted to the drug release data, and the results are cumulatively presented in Figure 7a-e. The drug release rate from the film was proportional to the amount of drug remaining in the film, and the R^2 value of 0.9821 for POS/PVA/SA-L-valine indicated first-order kinetics, indicating that the drug release from the film was dependent on the loading concentration. This fact was also confirmed by the high R^2 values in the Higuchi model (Figure 7b). A positive value is required for b, which stands for the drug's 'burst effect' or quick release. The Korsmeyer-Peppas equation and the interpretation of release exponents (n) are the most effective ways to understand the mechanisms of controlled drug release from materials that swell. The medication release mechanism that characterizes the release system is indicated by the value of 'n'. The 'n' value of 1.269 indicates super case-II transport drug release from the films.[22] Diffusion and swelling control the drug release mechanism in super Case-II transport scenarios.[23] It is also possible that a mix of erosion and dissolution, or other drug release mechanisms, plays a role in release kinetics. Thus, the in-vitro release profile of posaconazole-loaded PVA/SA-L-valine was determined. The film demonstrated effective drug release for topical application, showing 96.01%, 98.23%, and 95.52% cumulative drug release at pH

3.4, 5.5, and 7.4, respectively, within 24 h, as illustrated in Figure 6. In vitro drug release tests were conducted at pH 3.4 (acidic), pH 5.5 (skin surface pH), and pH 7.4 (physiological state) to evaluate the film's applicability to topical antifungal agents. According to the test results, the cumulative drug release rates within 24 hours were 96.01%, 98.23%, and 95.52%, respectively. Notably, the highest release rate was observed at pH 5.5, which is very close to the natural pH value of human skin. This suggests that the polyvinyl alcohol/L-valine film loaded with posaconazole is suitable for topical antifungal treatment because it enables efficient drug release under conditions similar to those of the skin. Therefore, this material is considered a promising candidate for future treatments of skin-related fungal infections. The response to external stimuli, such as pH, can be utilized to control drug delivery from POS/PVA/SA-L-valine. Figure 8 shows a schematic diagram of the stimulus-responsive drug release mechanism from a POS/PVA/SA-L-valine film carrying posaconazole. This diagram illustrates that drug release is enhanced under acidic conditions (pH 3.4 and 5.5) compared to physiological pH (7.4).

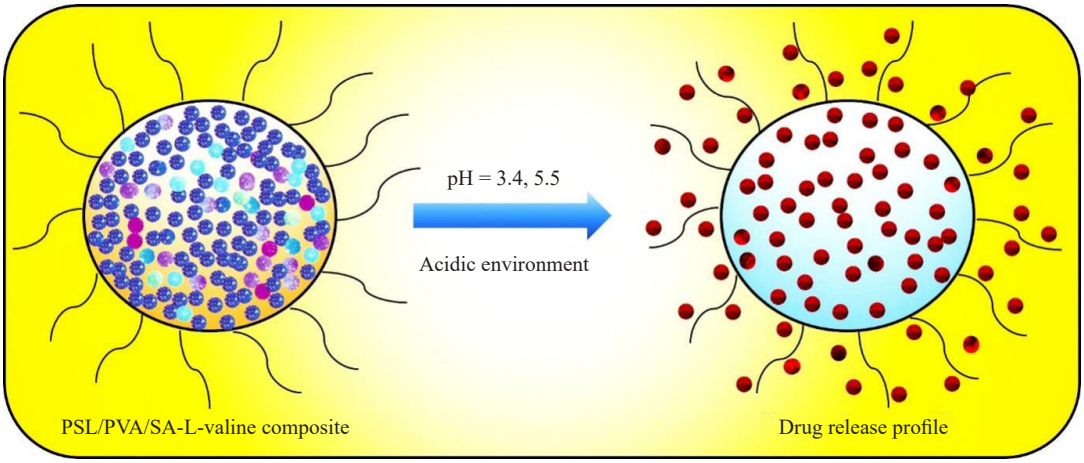


Figure 8. Drug delivery of PVA/SA-L-valine at pH

3.6 *Docking studies*

A potential target for the studies could be the lipid transfer protein Sec14p. Sec14-like Phosphatidylinositol Transfer Proteins (PITPs) integrate diverse aspects of intracellular lipid metabolism with stimulated phosphatidylinositol-4-phosphate production and are discriminating portals for interrogating phosphoinositide signalling. The efficient secretion of pathogenicity factors requires Sec14p, the major PITP, to perform essential functions in various pathogenic fungi. It is an attractive target for antifungal drugs because it is druggable.

In molecular drug docking experiments, POS was used as a ligand to dock with the active sites of the yeast Sec14p protein structure and the protein targets of NPPM481 [ID: 7ZGC]. Figure 9 displays the 3D structure of the target protein after removing the residual water molecule from crystallization.

The development of next-generation antifungal drugs can be achieved by targeting Sec14 PITPs. The structures of Sec14 bound to Small Molecule Inhibitors (SMIs) of diverse chemotypes have been reported. This study provides critical information required for the future structure-based design of next-generation lead compounds directed against Sec14 PITPs of virulent fungi.

The binding affinity of the posaconazole drug against the 7ZGC receptors is listed in Table 1. The study revealed that posaconazole (ligand) has a strong bonding energy of -4.1, and its interacting residues have a conventional hydrogen bond (ASN 208, SER 198).

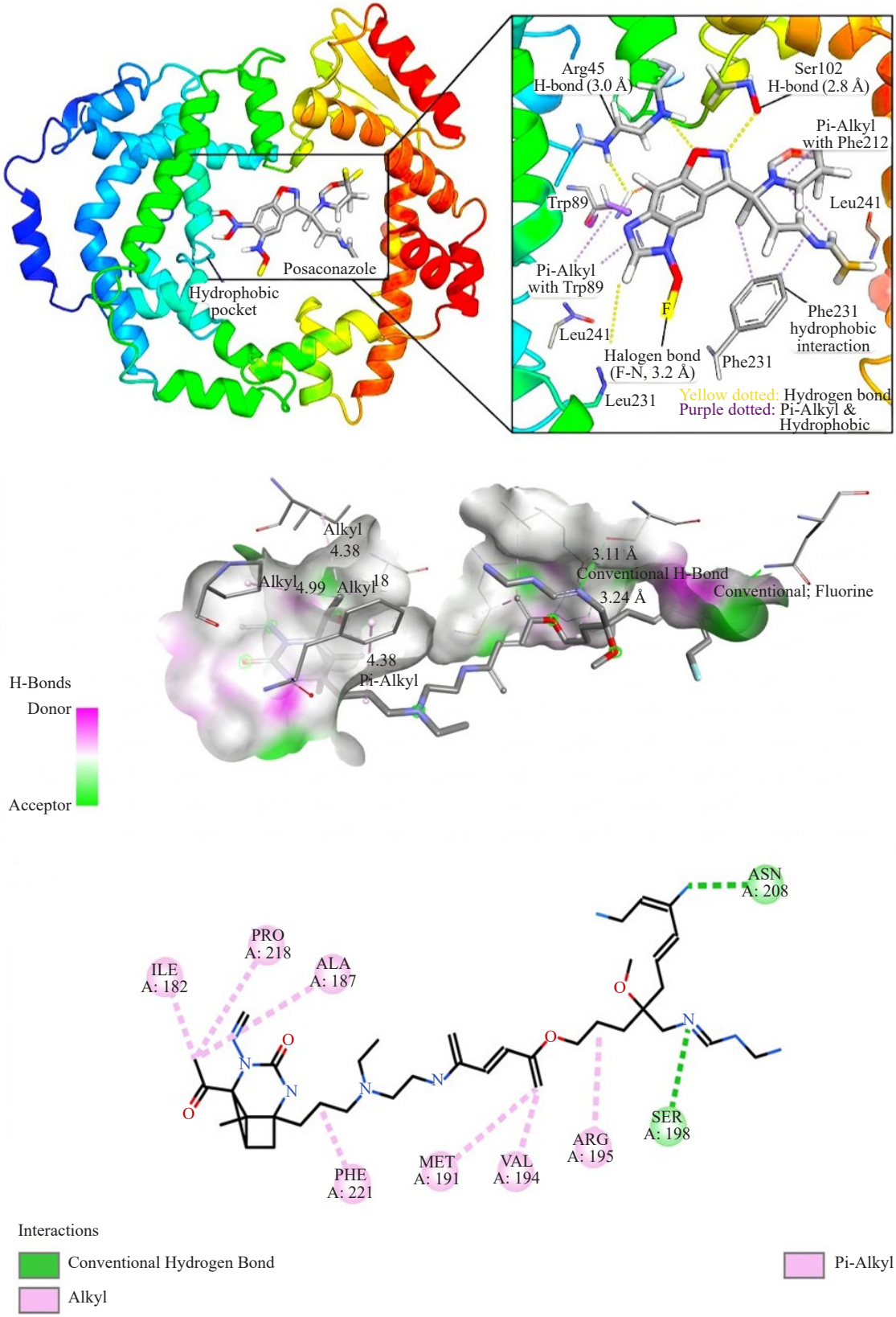


Figure 9. 3D image of PSL drug docked with 7ZGC protein

Table 1. Docking results of the POS towards 7ZGC

Ligand/Protein code	Posaconazole/7ZGC
Binding energy	-4.1
Ligand efficiency	-0.09
Inhib constant	547.76
Intermol energy	-7.43
Vdw_hb_desolv_energy	-7.37
Electrostatic energy	-0.06
Total internal	-1.94
Torsional energy	2.98
Unbound energy	-1.94
Ref RMS	61.71

4. Conclusion

In conclusion, using the solvent evaporation method, we successfully developed posaconazole-loaded PVA/SA-L-valine composite films for controlled local drug delivery. Structural and physicochemical characterization by FT-IR and XRD confirmed effective drug incorporation and favorable drug interactions within the polymer matrix. FE-SEM analysis also revealed a dense film morphology with structural features supporting controlled-release behavior. The developed posaconazole-containing polyvinyl alcohol/L-valine film demonstrated effective drug release under different pH conditions, showing release rates of 96.01%, 98.23%, and 95.52% at pH 3.4, 5.5, and 7.4, respectively, within 24 h. The maximum release rate observed at pH 5.5 (the pH of the skin surface) indicates suitability for topical application. The optimized formulation exhibited a sustained release profile following Super Case-II transport and showed improved antifungal activity against Candida species, suggesting its effective potential in the topical treatment of fungal infections and promising future applications in skin-related antifungal therapy. Furthermore, molecular docking studies with the lipid transfer protein Sec14p from *Saccharomyces cerevisiae* confirmed favorable binding interactions, indicating that posaconazole retained its biological activity after formulation. Overall, the developed system represents a promising platform for controlled topical drug delivery with improved drug release characteristics and enhanced patient compliance.

Acknowledgment

We thank RUSA 2.0 for funding this research work.

Author contribution

R. Naveenkumar contributed to collecting primary data, designing the experiment, performing the experimental analysis, overall manuscript writing, formal analysis, and finalizing. P. R. Nithiyasri was involved in experimental analysis, contributing to the draft and reviewing the draft.

B. Karthikeyan was involved in the supervision, resources, and provided the necessary facilities.

Funding

The project RUSA 2.0-100-E-002 funded this research work.

Conflict of interest

The authors declare no conflict of interest in this research work.

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