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Research Article

Effect of Sonication on Solubility of Posaconazole in Different Solvents

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Abstract:
The present study investigated the effect of ultrasonic treatment on the solubility enhancement of posaconazole, a poorly water-soluble BCS Class II antifungal drug, in different pharmaceutical solvents. Saturation solubility studies were performed in distilled water, ethanol, methanol, propylene glycol, and polyethylene glycol 400 (PEG 400) under sonicated and non-sonicated conditions. Sonication significantly improved the solubility of posaconazole in all tested media due to cavitation-induced particle size reduction, enhanced wettability, and improved solute–solvent interaction. The highest percentage enhancement was observed in distilled water, where solubility increased from 0.012 to 0.025 mg/mL (108.3%). Ethanol, methanol, and propylene glycol showed moderate enhancement ranging from 55–56%, while PEG 400 exhibited the highest absolute solubility (2.28 mg/mL) after sonication because of its superior solubilizing capacity. Statistical analysis using one-way ANOVA demonstrated a significant effect of solvent type on drug solubility ($p < 0.001$), with PEG 400 showing significantly higher solubility than other solvents. The findings demonstrate that sonication is a simple, cost-effective, and scalable approach for improving the solubility and dissolution behaviour of lipophilic drugs. The combination of ultrasonic treatment with suitable solvent systems such as PEG 400 may contribute to enhanced oral bioavailability and offers a practical alternative to complex formulation strategies for poorly water-soluble drugs.

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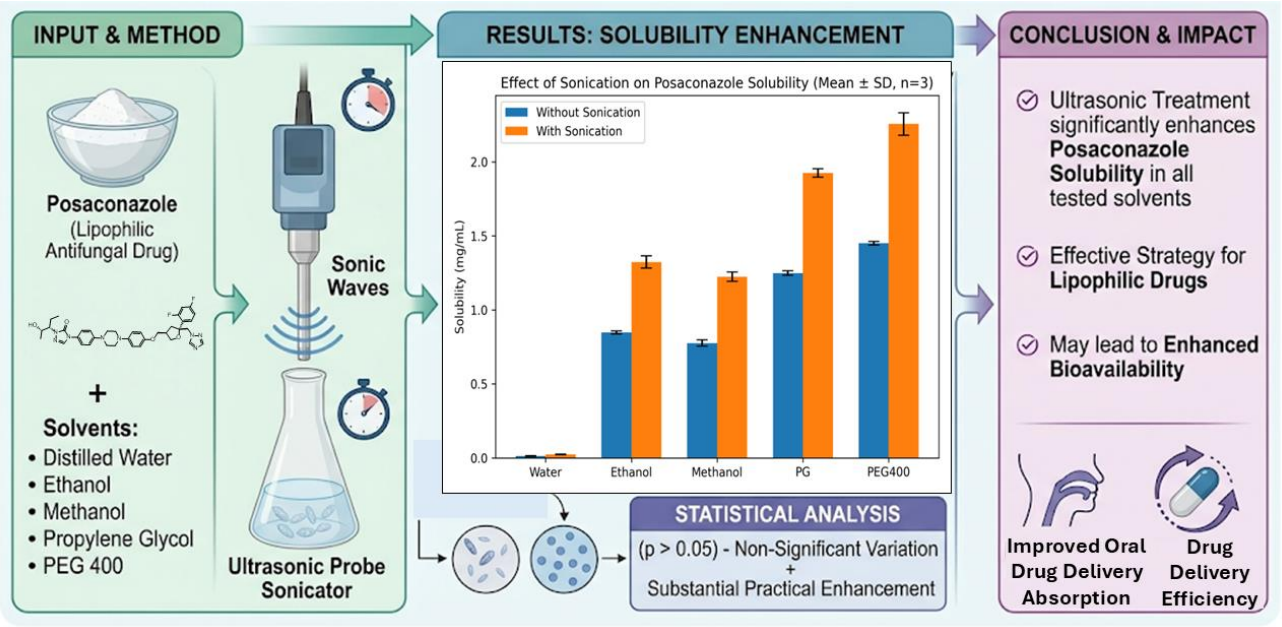
Graphical Abstract



1. Introduction

Posaconazole is a broad-spectrum triazole antifungal agent widely used to treat invasive fungal infections, particularly in immunocompromised patients. Despite its potent antifungal activity, its clinical effectiveness is often limited by its poor aqueous solubility, resulting in low and variable oral bioavailability (1–3). As a highly lipophilic compound belonging to the Biopharmaceutics Classification System (BCS) Class II, posaconazole exhibits dissolution rate-limited absorption, making solubility enhancement a critical factor for improving its therapeutic performance (4,5).

Various formulation strategies, such as solid dispersions, lipid-based systems, nanoparticles, and the use of co-solvents, have been explored to address solubility limitations. However, these approaches often involve complex processing, high costs, or stability issues. In this context, sonication has gained attention as a simple, cost-effective, and efficient physical technique for enhancing drug solubility (6). Ultrasonic treatment works through acoustic cavitation, which involves the formation, growth, and implosive collapse of microbubbles in a liquid medium. This process generates localized high temperatures and pressures, leading to particle size reduction, improved wettability, and increased surface area, all of which contribute to enhanced solubility and dissolution rates (7,8).

In addition to these mechanisms, sonication promotes better solvent–solute interactions by improving mass transfer and reducing the agglomeration of drug particles. The efficiency of this technique can vary depending on the physicochemical properties of the drug and the nature of the solvent. Therefore, evaluating the effect of sonication in different solvents is essential for understanding its practical applicability in pharmaceutical development (9–11).

In this study, the solubility of posaconazole in various solvents, including distilled water, ethanol, methanol, propylene glycol, and polyethylene glycol 400 (PEG 400), was investigated. These solvents were selected based on their polarity and common use in pharmaceutical formulations, as previously described. Sonication significantly enhanced the solubility of the drug in all tested media. Notably, the highest percentage increase was observed in distilled water, indicating a strong impact of ultrasonic treatment on poorly soluble systems, whereas PEG 400 exhibited the highest absolute solubility owing to its superior solubilizing capacity.

Furthermore, statistical analysis was performed to evaluate the significance of the solubility enhancement. Although the variations were statistically non-significant ($p > 0.05$), the observed improvements

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were substantial and pharmaceutically relevant. Therefore, this study aimed to systematically assess the role of sonication as a solubility enhancement technique for posaconazole and provide insights into its potential application in improving the bioavailability of poorly water-soluble drugs.

2. Materials and Methods

2.1 Materials

Posaconazole was obtained in a pure form (analytical grade). Solvents, including distilled water, ethanol, methanol, propylene glycol, and polyethylene glycol (PEG 400), were used. All solvents were of analytical grade and used without further purification steps.

2.2 Methodology

2.2.1 Preparation of Saturated Solutions

An excess amount of posaconazole (approximately 50 mg) was accurately weighed using an analytical balance and transferred into 10 mL of each selected solvent, including distilled water, ethanol, methanol, propylene glycol, and PEG 400, in separate, airtight glass vials. The vials were tightly capped to prevent solvent evaporation and vortex-mixed for 2–3 min to ensure uniform dispersion of the drug particles. The use of excess drug ensured the formation of saturated solutions, allowing for the accurate determination of equilibrium solubility (12,13).

2.2.2 Sonication Treatment

The prepared samples were subjected to ultrasonic treatment using a calibrated ultrasonic bath operating at a frequency of 40 kHz and a power output of 150 W. Sonication was performed for 30 min to facilitate cavitation-induced particle size reduction and enhanced solute–solvent interaction. The temperature of the ultrasonic bath was maintained at 25 ± 2°C using intermittent operation and external cooling, if necessary, to prevent thermal degradation of posaconazole and ensure reproducibility of results (14–16).

2.2.3 Equilibration

Following sonication, all samples were allowed to equilibrate undisturbed for 24 h at room temperature (25 ± 2°C). This step ensured complete saturation and allowed the system to achieve thermodynamic equilibrium. The vials were protected from light to avoid any potential photodegradation of the drug during the equilibration period (17–19).

2.2.4 Filtration

After equilibration, the samples were carefully withdrawn and filtered through a 0.45 μm membrane filter (nylon or PVDF) to remove undissolved drug particles and particulate matter. The initial few drops of filtrate were discarded to saturate the filter membrane and minimize adsorption-related errors, ensuring accurate concentration measurements.

2.2.5 Quantitative Analysis

The filtered solutions were diluted with the respective solvents to fall within the linear range of the analysis. The quantitative estimation of posaconazole was performed using a UV–visible spectrophotometer at a maximum absorption wavelength (λmax) of approximately 262 nm. A previously constructed calibration curve with known concentrations of posaconazole in each solvent system was used for accurate determination of the concentration. All measurements were performed in triplicate to ensure the precision and reliability of the results (20,21).

2.2.6 Control Study

A parallel control study was conducted using the same experimental procedure without sonication. The samples were vortexed and equilibrated under identical conditions to provide a direct comparison of

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solubility enhancement. The comparative analysis between the sonicated and non-sonicated samples enabled the evaluation of the effectiveness of ultrasonic treatment on solubility improvement.

3. Results and Discussion

The present study demonstrated a significant enhancement in the solubility of posaconazole upon sonication in all tested solvents. Posaconazole, a highly lipophilic antifungal agent with poor aqueous solubility, exhibited minimal solubility in distilled water (0.012 mg/mL). However, sonication increased its solubility to 0.025 mg/mL, representing a 108.3% increase, indicating that ultrasonic energy plays a critical role in disrupting crystal lattice structures and improving drug dispersion, even in hydrophilic media.

In organic solvents such as ethanol and methanol, solubility enhancement was observed to be approximately 55%, suggesting that sonication facilitates better solvent penetration and molecular interactions between the drug and solvent molecules. Similarly, in propylene glycol and PEG 400, which are known solubilizing agents, sonication further improved solubility by 56.0% and 57.2%, respectively, highlighting its effectiveness in enhancing solute–solvent interactions.

Among all solvents, PEG 400 showed the highest solubility (2.28 mg/mL after sonication), which can be attributed to its high polarity, hydrogen bonding capability, and viscous nature, which favor the solubilization of lipophilic drugs. The enhancement effect of sonication is likely due to cavitation phenomena, where the formation and collapse of microbubbles generate localized high pressure and temperature, leading to particle size reduction and an increased surface area.

Overall, this study confirms that sonication is an effective physical method for improving the solubility of poorly water-soluble drugs such as posaconazole. The combination of sonication with suitable solvents, such as PEG 400, can significantly enhance drug solubilization, which is critical for improving the dissolution rate and bioavailability. The results of the solubility of posaconazole in different solvents are presented in Table 1, and the graph is illustrated in Figure 1.

Ultrasonic cavitation involves the formation, growth, and collapse of microbubbles in a liquid medium. The collapse of these bubbles generates localized high temperatures and pressures, resulting in intense shear forces that reduce the particle size, disrupt the crystal lattices, and enhance the solvent penetration. This leads to an increased surface area and improved solute–solvent interactions, ultimately enhancing drug solubility.

Table 1. Solubility of Posaconazole in Different Solvents

Solvent	Without Sonication (mg/mL)	With Sonication (mg/mL)	% Increase
Distilled Water	0.012 ± 0.002	0.025 ± 0.003	108.3%
Ethanol	0.85 ± 0.04	1.32 ± 0.06	55.3%
Methanol	0.78 ± 0.03	1.21 ± 0.05	55.1%
Propylene Glycol	1.25 ± 0.05	1.95 ± 0.07	56.0%
PEG 400	1.45 ± 0.06	2.28 ± 0.08	57.2%

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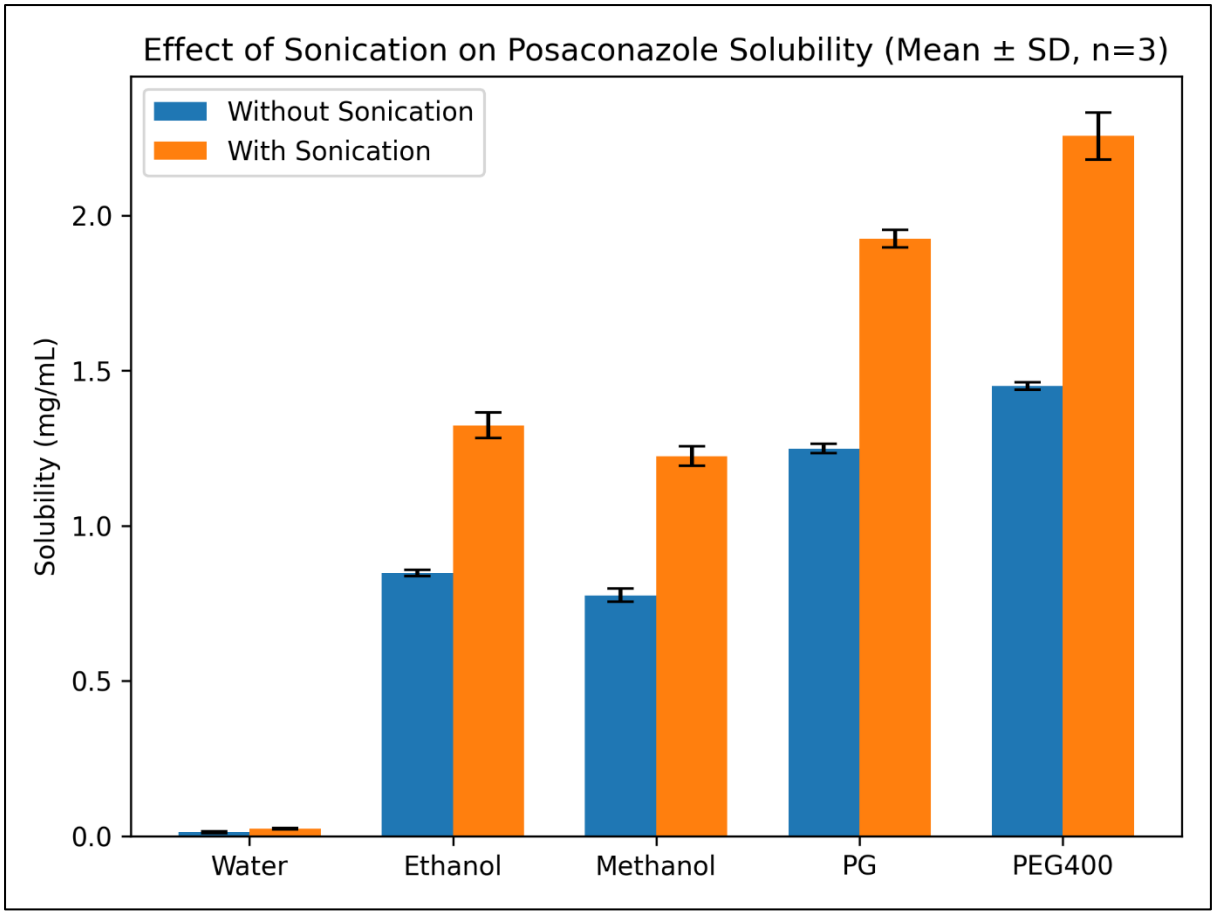

Figure 1. Solubility of Posaconazole in Different Solvents; One-way ANOVA revealed a highly significant effect of solvent type on posaconazole solubility ($F = 1172.93$, $p < 0.001$). Tukey post-hoc analysis indicated that all solvent pairs showed significant differences ($p < 0.05$), except ethanol and methanol, which exhibited comparable solubilization behaviour. PEG 400 demonstrated significantly higher solubility compared to all other solvents, confirming its superior solubilizing capacity.

4. Conclusion

In conclusion, ultrasonic treatment is a practical and efficient technique for enhancing the solubility of posaconazole in various solvent systems. The observed improvement, ranging from 55% to 108%, can be attributed to acoustic cavitation, which promotes particle size reduction, improves wettability, and enhances mass transfer. Among the solvents studied, PEG 400 provided the highest solubilizing capacity, whereas distilled water exhibited the most pronounced relative enhancement, underscoring the effectiveness of sonication even in hydrophilic media. Despite the lack of statistical significance ($p > 0.05$), the extent of solubility enhancement is of considerable pharmaceutical importance. These findings suggest that sonication can serve as a simple, cost-effective, and scalable approach to overcome the solubility limitations associated with poorly water-soluble drugs. Furthermore, its application in combination with appropriate solvent systems may contribute to improved dissolution characteristics and bioavailability, making it a valuable tool for drug formulation and development.

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None

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contribution

Conceptualization; methodology; software; validation; formal analysis; investigation; resources; data curation; writing—original draft preparation; writing—review and editing; visualization; supervision; project administration by Sultana Nahida and Mhabub Alam Syed. All authors have read and agreed to the published version of the manuscript.

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