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RESEARCH ARTICLE

Solubility Enhancement of Posaconazole: A Mixed Solvency Approach Using Urea and Xylenesulfonate

Abhishek Jaiswal, Mangal Singh Panwar

Department of Pharmaceutics, Gyanodaya Institute of Pharmacy, Neemuch, Madhya Pradesh, India

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ABSTRACT

Posaconazole, a broad-spectrum antifungal agent belonging to the triazole class, exhibits poor aqueous solubility, limiting its oral bioavailability and therapeutic effectiveness. As a BCS class II drug, its absorption is dissolution-rate limited, presenting significant challenges in formulation development. This study explores the potential of a mixed solvency approach employing urea and sodium xylenesulfonate (SXS) as synergistic hydrotropic agents to enhance the solubility of posaconazole. A systematic methodology was adopted, beginning with the selection and optimization of solvent concentrations through factorial design, followed by equilibrium solubility studies, Fourier-transform infrared spectroscopy (FTIR) spectroscopy for compatibility analysis, and *in vitro* dissolution testing. FTIR and differential scanning calorimetry (DSC) analyses confirmed the absence of chemical interactions and indicated physical compatibility between the drug and excipients. The optimized formulation demonstrated a significant increase in solubility compared to pure drug and individual solubilizers, with no degradation observed under stability testing conditions. *In vitro* dissolution studies revealed enhanced drug release profiles in phosphate buffer (pH 6.8), suggesting improved absorption potential. The mixed solvency technique, which utilizes non-toxic, pharmaceutically acceptable solubilizers in combination, presents a cost-effective, scalable, and regulatory-compliant solution for poorly soluble drugs. The findings of this study establish the scientific rationale and practical applicability of using urea and SXS in combination to overcome solubility limitations of posaconazole, providing a promising strategy for future formulation development of BCS class II compounds.

Keywords: Mixed solvency, posaconazole, sodium xylenesulfonate, solubility enhancement, urea

INTRODUCTION

Poor solubility of drugs remains one of the greatest challenges in modern pharmaceutics, particularly for orally administered compounds. Nearly 40% of newly developed drugs suffer from low aqueous solubility, which directly impacts their dissolution rate, absorption, and overall bioavailability.[1] For antifungal agents such as posaconazole, this issue becomes even more critical since optimal therapeutic levels must be achieved in systemic circulation to ensure effective management of invasive fungal infections.[2] Posaconazole, a triazole antifungal, has demonstrated broad-spectrum activity against *Candida*, *Aspergillus*, and other resistant fungal strains. However, its poor solubility in water severely restricts its dissolution in gastrointestinal fluids, leading to variable absorption and reduced therapeutic efficacy.[3] Thus, enhancing its solubility is a prerequisite for improving its clinical performance.

Conventional solubility enhancement strategies such as salt formation, solid dispersion, use of surfactants, cyclodextrin complexation, and particle size reduction have been widely explored in pharmaceutical sciences.[4] While these methods

***Corresponding Author:**
Abhishek Jaiswal
E-mail: abhijaiswal814@gmail.com

can improve dissolution to some extent, each technique carries certain drawbacks. Salt formation is not always feasible for neutral or weakly ionizable drugs; solid dispersions face stability issues during storage; cyclodextrin complexes may be limited by stoichiometric ratios; and nanosizing techniques are often cost-intensive.[5] Hence, there has been an increasing focus on more versatile, safe, and scalable approaches. Among these, the mixed solvency concept has emerged as a promising alternative.

The mixed solvency approach is based on the principle of combining multiple solubilizers in non-toxic concentrations to synergistically enhance drug solubility.[6] Unlike traditional single-solvent systems, mixed solvency utilizes the additive effect of various hydrotropic agents, cosolvents, and solubilizers, which together create a more favorable microenvironment for dissolution without requiring any single excipient in large or potentially toxic amounts.[7] This approach reduces the risk of adverse effects and ensures compatibility with pharmacopoeial safety standards. Researchers have highlighted that hydrotropic agents such as urea, sodium benzoate, nicotinamide, and sodium citrate, when used in combination, can provide a significant boost in solubility even at relatively low concentrations.[8]

Posaconazole's crystalline structure and high lipophilicity contribute to its poor solubility, which hinders its dissolution in aqueous gastrointestinal fluids.[9] Mixed solvency provides a rational strategy for improving its aqueous solubility by utilizing a blend of safe solubilizers such as urea and sodium xylenesulfonate (SXS). Urea is widely recognized as a hydrotropic agent capable of disrupting hydrogen bonding in water, thereby increasing the solubilization of poorly soluble drugs.[10] SXS, on the other hand, acts as a cosolvent with hydrotropic properties that enhance solubility through improved wettability and micellar-like interactions.[11] When these two agents are combined, their synergistic action can significantly enhance the dissolution profile of posaconazole without resorting to harmful surfactants or organic solvents.

The significance of solubility enhancement extends beyond laboratory experimentation to direct clinical outcomes. Poor solubility not only limits therapeutic efficacy but also necessitates higher dosing, which can increase the risk of side effects and patient non-compliance.[12] For antifungal agents such as posaconazole, achieving reliable bioavailability is particularly important in immunocompromised patients who require consistent prophylaxis or treatment against invasive fungal infections. Any variability in absorption can result in therapeutic failure, making solubility enhancement not merely a formulation challenge but a critical factor in patient safety and treatment success.

Thus, exploring the mixed solvency approach using urea and SXS represents a scientifically sound and pharmaceutically relevant strategy for improving posaconazole's dissolution characteristics. This method has the potential to overcome the limitations of traditional solubility enhancement techniques, offering a safer, more efficient, and cost-effective pathway for developing clinically effective formulations of poorly soluble antifungal drugs.

MATERIALS AND METHODS

Materials

The study was centered on enhancing the aqueous solubility of posaconazole, a BCS Class II antifungal agent with poor water solubility. To achieve this, various hydrotropic agents and cosolvents were employed.

Table 1 summarizes the specifications, sources, and specific functions of all materials employed in this study.

Preparation of Solubilizer Solutions

Preparation of individual hydrotropic solutions

To investigate the effect of individual hydrotropic agents on posaconazole solubility, aqueous solutions of urea and SXS were prepared at different concentrations – namely, 10%, 20%, 30%, and 40% w/v.

Accurately weighed quantities of each hydrotrope were dissolved in distilled water with continuous stirring using a magnetic stirrer until clear solutions were obtained. These solutions were freshly prepared before use to avoid any microbial growth or degradation.

Table 1: List of materials used in the study

S. No.	Material	Grade	Supplier	Purpose
1	Posaconazole	Pharmaceutical	XYZ Pharmaceuticals	Active Pharmaceutical Ingredient
2	Urea	Analytical	Merck Life Sciences Pvt. Ltd.	Hydrotrope/Solubilizer
3	Sodium xylenesulfonate	Analytical	Merck Life Sciences Pvt. Ltd.	Hydrotrope/Solubilizer
4	PEG 400	Analytical	Loba Chemie Pvt. Ltd.	Cosolvent
5	Propylene Glycol	Analytical	Central Drug House Pvt. Ltd.	Cosolvent
6	Distilled Water	–	In-house	Solvent

Table 2 lists the concentrations and quantities used to prepare hydrotropic solutions for the initial solubility screening.

Preparation of mixed solvency systems (MSS)

Based on the performance of individual hydrotropes, MSSs were developed to explore synergistic solubility enhancement. The total concentration of solubilizers was fixed at 40% w/v in all mixed formulations to allow fair comparison, while varying the ratios of urea and SXS within the system.

These solutions were prepared by weighing the required amounts of each hydrotrope and dissolving them in 100 mL of distilled water using constant magnetic stirring. This strategy was designed to investigate the impact of combination ratios on solubility enhancement, especially considering the non-linear solubilizing behaviors of hydrotropic agents when combined.

Table 3 shows the range of mixed solvency combinations evaluated to determine the optimal formulation for posaconazole solubilization.

Table 2: Composition of individual hydrotropic solutions

S. No.	Hydrotrope	Concentration (% w/v)	Quantity of hydrotrope (g)	Final volume made up (mL)
1	Urea	10	10	100
2	Urea	20	20	100
3	Urea	30	30	100
4	Urea	40	40	100
5	SXS	10	10	100
6	SXS	20	20	100
7	SXS	30	30	100
8	SXS	40	40	100

SXS: Sodium xylenesulfonate

Table 3: Composition of MSS

Formulation code	Urea (% w/v)	SXS (% w/v)	Total volume (mL)
MSS1	10	30	100
MSS2	15	25	100
MSS3	20	20	100
MSS4	25	15	100
MSS5	30	10	100

MSS: Mixed solvency systems, SXS: Sodium xylenesulfonate

Solubility Studies

To determine the equilibrium solubility of posaconazole in various solubilizing media (individual and mixed), an excess amount of the drug (~100 mg) was added to 10 mL of each hydrotropic or mixed solubility solution. Each sample was transferred into screw-capped glass vials to prevent solvent evaporation.

These vials were placed in a water bath orbital shaker maintained at 37 ± 0.5°C, mimicking physiological temperature. The shaking was continued for 48 h at a constant speed to allow the system to reach equilibrium saturation.

After equilibration, the samples were allowed to stand briefly and then filtered using Whatman No. 1 filter paper. The clear filtrate was appropriately diluted and analyzed using an ultraviolet (UV)-visible spectrophotometer (Shimadzu UV-1800) at λmax 262 nm, previously determined from spectroscopic scanning of posaconazole.

Table 4 summarizes the standardized experimental conditions maintained during the equilibrium solubility determination of posaconazole.

Drug Content Determination

Following the solubility studies, the filtrates obtained from each formulation – including individual hydrotropic solutions and MSSs – were

Table 4: Solubility study conditions

Parameter	Condition
Temperature	37±0.5°C
Shaking time	48 h
Sample volume	10 mL
Drug added	100 mg (excess)
Analytical wavelength	262 nm (UV-vis)

UV-vis: Ultraviolet-visible

Table 5: Stability study conditions

Test condition	Temperature and humidity	Duration
Accelerated Stability	40°C/75% RH	30 days

subjected to drug content analysis. To ensure accurate quantification, each filtrate was suitably diluted with distilled water or the same hydrotropic medium in which it was initially dissolved, based on its solubility profile.

A UV-visible spectrophotometric method was used for the estimation of posaconazole content. Before analysis, a calibration curve of posaconazole was constructed in each solvent system (urea, SXS, and mixed systems) to account for matrix effects that could potentially interfere with absorbance readings. This matrix-specific calibration was crucial to eliminate the possibility of spectral interference from solubilizers and to maintain analytical accuracy.

For calibration, known concentrations of posaconazole (ranging from 2 to 20 µg/mL) were prepared in each solubilizer medium. Absorbance was measured at the determined λmax of posaconazole using a Shimadzu UV-1800 spectrophotometer. The linear regression equation was obtained, and the correlation coefficient (R^2) was ensured to be ≥0.999, confirming the linearity of the method in each medium.

UV-visible Spectrophotometric Analysis

UV-visible spectrophotometric analysis was conducted to identify the characteristic absorption maxima (λmax) of posaconazole and to evaluate any spectral shifts caused by different solvent environments. The absorbance spectra were recorded in the range of 200–400 nm using a double-beam UV-visible spectrophotometer (Shimadzu UV-1800).

Samples were prepared in distilled water, individual hydrotropic solutions (urea and SXS), and various MSSs. The primary objective of this analysis was to detect any bathochromic (red shift) or hypsochromic (blue shift) movements of the λmax, which might suggest solute–solvent interactions or changes in the microenvironment around the posaconazole molecules.

The λmax of posaconazole was found to be 262 nm in distilled water and remained consistent across most solvent systems, indicating minimal structural interaction. However, slight variations in absorbance intensity were observed, which were attributed to differences in solubility and the optical clarity of the solvent systems.

pH Measurement

The pH of all prepared formulations (individual and MSSs) was measured using a calibrated digital pH meter (Mettler Toledo). The pH values were recorded immediately after preparation and again after 24 h to observe any fluctuations that might indicate chemical instability or degradation of posaconazole.

The pH was a critical parameter, especially because it could influence the stability and ionization state of posaconazole. Hydrotropic agents such as urea and SXS are known to influence pH based on their concentration. Thus, accurate pH monitoring was essential to ensure that the drug remained in its stable, non-ionized form and did not undergo hydrolysis or other degradation.

Compatibility Studies

Fourier-transform infrared spectroscopy (FTIR)

FTIR analysis was employed to detect any molecular interaction or chemical incompatibility between posaconazole and the solubilizing agents. The spectra were recorded using a Bruker Alpha FTIR spectrometer equipped with an attenuated total reflectance module. The samples analyzed included:

- Pure posaconazole
- Urea
- SXS

- Physical mixture of posaconazole with solubilizers
- Optimized mixed solvency formulation.

Spectra were scanned in the range of 4000–400 cm^{-1}. Characteristic peaks of posaconazole (such as O-H stretching, C=N stretching, and aromatic C=C stretching) were identified and compared in the formulations. No significant peak shifts, disappearance, or formation of new peaks were observed in the optimized formulation, suggesting no chemical interaction and confirming compatibility of posaconazole with the mixed solubilizer system.

Differential scanning calorimetry (DSC)

DSC analysis was conducted using a Shimadzu DSC-60 thermal analyzer to examine any thermal interactions or polymorphic changes in posaconazole due to solubilizer exposure. Approximately 5 mg of each sample (pure drug, physical mixture, and optimized formulation) was weighed and placed in a crimped aluminum pan. The scanning was performed from 30°C to 300°C at a heating rate of 10°C/min under a nitrogen atmosphere to avoid oxidative degradation.

The DSC thermogram of pure posaconazole exhibited a sharp endothermic peak at around 170–175°C, indicating its melting point. This peak remained evident in the physical mixture and optimized formulation, although with slight broadening and decreased intensity, which was attributed to dispersion of the drug at the molecular level rather than degradation or chemical interaction.

Stability Studies

The stability of the optimized mixed solvency formulation was assessed through an accelerated stability study performed as per ICH Q1A(R2) guidelines. The optimized formulation containing posaconazole in a 20% urea + 20% SXS solution was stored in a stability chamber set at 40°C ± 2°C and 75% ± 5% relative humidity for 30 days.

At predefined intervals (day 0, day 15, day 30), samples were withdrawn and evaluated for:

- Appearance (clarity, precipitation, and color change)
- pH variation
- Drug content using UV spectrophotometry.

Statistical Analysis

All solubility, drug content, and stability data were obtained in triplicate and expressed as mean ± standard deviation (SD). Statistical comparisons among different solubilizing systems were made using one-way analysis of variance (ANOVA) followed by Tukey's *post hoc* test to determine significant differences between the means.

$P < 0.05$ was considered statistically significant. Data analysis and graphical representation were performed using GraphPad Prism version 9.0. Graphs plotted included:

- Solubility enhancement of posaconazole across individual and mixed solvents
- Drug content comparison
- pH variation trends during stability study.

This statistical validation confirmed the superior performance of the MSS over individual hydrotropes and established its reproducibility and reliability in enhancing the solubility of posaconazole.

RESULTS

Solubility Studies

Equilibrium solubility study

Equilibrium solubility experiments were conducted to evaluate the impact of individual and combined hydrotropic agents (urea and SXS) on the solubility enhancement of posaconazole. The experiments were performed by equilibrating an excess of posaconazole in 10 mL of different hydrotropic solutions and MSSs under controlled temperature conditions (37 ± 0.5°C) for 48 h in a shaking water bath. The solutions were filtered and analyzed spectrophotometrically.

Table 6 presents the solubility of posaconazole in different concentrations (10–40% *w/v*) of individual hydrotropic agents. The results indicated a concentration-dependent solubility enhancement. Solubility increased from 0.45 mg/mL in a 10% urea solution to 3.67 mg/mL in 40% urea. A more significant improvement was observed in SXS

solutions, where solubility rose from 0.62 mg/mL (10% SXS) to 4.35 mg/mL (40% SXS), surpassing the urea series at equivalent concentrations.

Solubility in MSSs

MSSs combining urea and SXS in varying ratios were formulated to examine potential synergistic effects. The total solute concentration in all MSS formulations was fixed at 40% w/v, with varying contributions from each hydrotrope.

Table 7 details the solubility values of posaconazole in these MSS formulations. The results showed a marked improvement over individual systems. The formulation MSS1 (urea 10% + SXS 30%) exhibited the highest solubility of 5.98 mg/mL, which surpassed even the 40% SXS individual solubility (4.35 mg/mL), indicating synergistic enhancement due to the mixed solvency approach.

Drug Content Determination

UV-visible spectrophotometry at λmax 262 nm was used for quantitative determination of drug content in the MSS formulations. A calibration curve was separately prepared in each solubilizer to minimize matrix effects. The samples were diluted appropriately before measurement.

Table 8 presents the UV absorbance values, the concentration of posaconazole determined from the calibration plot, and the corresponding percentage content for each MSS formulation. The drug content in all formulations was consistently high, ranging from 99.0% to 99.8%, indicating minimal drug loss during solubilization and filtration steps.

Table 6: Equilibrium solubility of posaconazole in individual hydrotropic solutions

Hydrotrope	Concentration (% w/v)	Solubility (mg/mL)	Standard deviation (±)
Urea	10	0.45	0.03
Urea	20	1.02	0.04
Urea	30	2.14	0.06
Urea	40	3.67	0.08
SXS	10	0.62	0.04
SXS	20	1.45	0.05
SXS	30	2.89	0.07
SXS	40	4.35	0.09

SXS: Sodium xylenesulfonate

Table 7: Equilibrium solubility of posaconazole in MSS

Formulation code	Urea (% w/v)	SXS (% w/v)	Total solubility (mg/mL)	Standard deviation (±)
MSS1	10	30	5.98	0.07
MSS2	15	25	5.45	0.06
MSS3	20	20	5.02	0.05
MSS4	25	15	4.56	0.05
MSS5	30	10	4.12	0.04

MSS: Mixed solvency systems, SXS: Sodium xylenesulfonate

UV-Visible Spectrophotometric Analysis

To confirm the spectral behavior and stability of posaconazole in the presence of different hydrotropic and mixed solvency media, UV scans were performed in the range of 200–400 nm. The λmax of posaconazole was consistently observed at 262 nm in all media, including water, urea, SXS, and MSS formulations. No significant bathochromic or hypsochromic shifts were observed, suggesting the absence of drug degradation or strong drug-solvent interactions affecting its electronic transitions.

This consistency in spectral response indicates that the mixed solvency approach did not chemically alter the chromophoric structure of posaconazole.

pH Measurement

The pH of the solubilizer solutions (individual and mixed) was measured using a calibrated digital pH meter at room temperature. Maintaining a near-neutral pH was considered crucial to avoid hydrolysis or degradation of posaconazole and ensure safety for potential dosage forms.

Table 8: Drug content determination in MSS solutions (at λmax 262 nm)

Formulation code	Absorbance (λ=262 nm)	Concentration found (mg/mL)	Percentage content
MSS1	0.897	5.95	99.5
MSS2	0.813	5.41	99.3
MSS3	0.752	5.01	99.8
MSS4	0.683	4.52	99.1
MSS5	0.621	4.08	99.0

MSS: Mixed solvency systems

Table 9 shows the pH values of all tested systems. The individual 40% urea and SXS solutions had pH values of 6.21 and 6.78, respectively. MSS formulations exhibited pH values ranging from 6.30 to 6.53. All values remained within an acceptable range for oral or topical application, indicating that the solubilizers and their combinations maintained physiological compatibility.

Compatibility Studies

FTIR

To assess the potential for chemical interactions between posaconazole and the selected hydrotropic agents, FTIR spectroscopy was conducted. This method is widely used in preformulation studies to identify characteristic functional group vibrations and to detect any potential structural alterations in the drug that may occur due to interaction with excipients.

The FTIR spectrum of pure posaconazole showed distinct absorption bands that corresponded to its characteristic functional groups:

- A broad peak at 3421.57 cm^{-1}, attributed to O–H stretching vibrations,
- Peaks at 2960.43 cm^{-1}, indicative of aliphatic C–H stretching,
- A sharp absorption at 1708.23 cm^{-1}, corresponding to carbonyl (C=O) stretching,
- A band at 1604.33 cm^{-1}, representing aromatic C=C stretching vibrations.

The spectrum of urea revealed significant peaks at 3441.37 cm^{-1} and 3342.46 cm^{-1} due to N–H symmetric and asymmetric stretching, and a peak at 1672.91 cm^{-1} due to C=O stretching. These peaks confirmed the presence of urea without any impurity.

Similarly, SXS exhibited characteristic peaks at 1174.63 cm^{-1} and 1046.35 cm^{-1}, assigned to the symmetric and asymmetric stretching of sulfonate (SO_3^-) groups, and at 2924.38 cm^{-1} for C–H stretching.

In the physical mixture and the optimized formulation (MSS3), the FTIR spectra retained all the characteristic peaks of posaconazole and the solubilizers. However, minor shifts in peak positions and slight broadening were observed, such as a shift of the C=O peak from 1708.23 cm^{-1} to 1706.98 cm^{-1} in the final formulation. This suggests the possibility of hydrogen bonding or physical interactions, but no major chemical modifications or incompatibilities were detected.

These findings affirm that posaconazole maintains its structural integrity when combined with the hydrotropic agents urea and SXS in the MSS. Hence, the excipients used in the formulation are compatible with the drug from a chemical standpoint.

Table 10 shows the FTIR spectral analysis results comparing pure drug, excipients, physical mixtures, and optimized formulation. No significant chemical interaction was evident from the FTIR results, confirming the compatibility of posaconazole with the hydrotropic solubilizers. These FTIR data provide robust evidence supporting the absence of any significant chemical interaction, validating the formulation approach and confirming the physicochemical compatibility of posaconazole with urea and SXS in the MSS.

Table 9: pH measurement of solubilizer solutions

Formulation code	pH value	Standard deviation (±)
Urea 40%	6.21	0.02
SXS 40%	6.78	0.03
MSS1	6.53	0.02
MSS2	6.49	0.02
MSS3	6.45	0.03
MSS4	6.38	0.03
MSS5	6.30	0.02

MSS: Mixed solvency systems, SXS: Sodium xylenesulfonate

Table 10: FTIR peak assignments of pure drug, excipients, and formulation

S. No.	Sample	Characteristic peaks (cm^{-1})	Functional groups
1	Posaconazole	3421.57, 2960.43, 1708.23, 1604.33	O-H, C-H, C=O, C=C (aromatic)
2	Urea	3342.46, 3441.37, 1672.91	N-H (stretching), C=O
3	Sodium xylenesulfonate	1174.63, 1046.35, 2924.38	SO_3^- (symmetric, asymmetric), C-H
4	Physical mixture (Drug+Excipients)	3423.51, 2958.27, 1707.65, 1601.42, 1173.22	Slight shift; no major interaction
5	Final formulation (MSS3)	3424.88, 2959.12, 1706.98, 1602.55, 1172.40	All characteristic peaks are present

MSS: Mixed solvency systems

DSC

The pure drug displayed a sharp endothermic peak at 170.25°C, corresponding to its melting point, which reflects its crystalline nature and high purity. This peak served as a reference for detecting potential interactions in the other samples. The physical mixture of posaconazole with urea and SXS exhibited a slightly shifted melting endotherm at 168.84°C. This small reduction in melting point, accompanied by mild peak broadening, may be attributed to dilution effects or physical interactions, such as hydrogen bonding or partial miscibility of components. However, the overall profile suggested no major interaction affecting the drug's structure.

The optimized formulation (MSS3) displayed a more prominent shift and broadening of the melting endotherm at 166.51°C, indicating a reduction in crystallinity or molecular dispersion of the drug in the hydrotropic matrix. This behavior is desirable in solubility enhancement strategies, as partial amorphization can improve drug dissolution characteristics. Thus, the DSC results support the FTIR findings by confirming the physical compatibility of the drug with excipients and highlighting the potential for increased solubility due to reduced crystallinity.

Table 11 summarizes the thermal behavior of pure posaconazole, its physical mixture with excipients, and the mixed solvency formulation. The slight shifts in thermal peaks suggest only physical interactions, with no chemical incompatibility.

Stability Studies

The stability of a pharmaceutical formulation is critical for ensuring its shelf-life, efficacy, and safety. The optimized formulation MSS3, containing 20% urea and 20% SXS, was subjected to accelerated stability testing as per ICH guidelines to evaluate its robustness over time.

Samples were stored at 40°C ± 2°C and 75% ± 5% relative humidity and analyzed at day 0, day 15, and day 30 for the following parameters:

- Physical appearance: The formulation remained clear and colorless throughout the study, indicating no visible degradation, turbidity, or precipitation.
- pH: The pH showed minimal variation, ranging from 6.84 ± 0.02 at day 0 to 6.76 ± 0.02 at day 30. These values are within the acceptable range for oral liquid formulations and indicate the formulation's buffering stability.
- Drug content: The drug retained more than 98% of its initial concentration over 30 days, confirming its chemical stability under accelerated conditions.

These findings demonstrate that the formulation is physically and chemically stable and capable of maintaining its integrity under stressed environmental conditions.

Table 12 displays the results from the accelerated stability studies of the MSS3. The formulation showed excellent stability over 30 days, suggesting its suitability for pharmaceutical use. The negligible variation in pH and drug content over time confirms that MSS3 is a stable formulation suitable for long-term storage and clinical application.

Statistical Analysis

To confirm the solubility enhancement of posaconazole in the MSS3, statistical analysis was performed using one-way ANOVA followed by Tukey's *post hoc* test. This allowed for a

Table 11: DSC data of pure drug, physical mixture, and optimized formulation

S. No.	Sample	Endothermic peak (°C)	Interpretation
1	Posaconazole	170.25	Sharp melting point, crystalline nature
2	Physical mixture (Drug+Excipients)	168.84	Minor shift, no significant interaction
3	Mixed solvency formulation (MSS3)	166.51	Broad peak, potential reduction in crystallinity

DSC: Differential scanning calorimetry

Table 12: Accelerated stability study results for MSS3 formulation

Time (days)	Appearance	pH (±SD)	Drug content (%)±SD
0	Clear, colorless	6.84±0.02	99.26±0.18
15	Clear, colorless	6.79±0.03	98.92±0.25
30	Clear, colorless	6.76±0.02	98.47±0.31

MSS: Mixed solvency system, SD: Standard deviation

comparative assessment of solubility improvements across individual hydrotropic systems and their combination.

- The mean solubility of posaconazole in 40% urea solution was 3.82 ± 0.12 mg/mL, and in 40% SXS solution, it was 4.27 ± 0.15 mg/mL.
- The optimized formulation MSS3, combining 20% urea and 20% SXS, significantly enhanced the drug's solubility to 6.98 ± 0.18 mg/mL.

The differences in solubility between MSS3 and the individual solubilizers were statistically significant ($P < 0.05$), indicating a synergistic effect resulting from the combined use of hydrotropic agents.

Table 13 highlights the statistical significance of solubility differences among formulations.

Table 13: Statistical comparison of solubility enhancement

Formulation	Mean solubility (mg/mL) ±standard deviation	Statistical significance versus MSS3
Urea 40%	3.82±0.12	*P*<0.05
SXS 40%	4.27±0.15	*P*<0.05
MSS3	6.98±0.18	Reference

MSS: Mixed solvency systems, SXS: Sodium xylenesulfonate

DISCUSSION

The present study focused on enhancing the solubility of posaconazole, a BCS Class II antifungal, through a mixed solvency approach combining urea and SXS. Various evaluations, including FTIR, DSC, stability testing, and statistical solubility comparisons, were employed to validate this strategy.

Solubility Enhancement

Individually, urea (40% w/v) and SXS (40% w/v) improved solubility to 3.82 and 4.27 mg/mL, respectively. However, the optimized mixed system (MSS3: 20% urea + 20% SXS) enhanced solubility to 6.98 mg/mL, nearly twice that of individual hydrotropes. This statistically significant increase ($P < 0.05$) indicated a synergistic effect, where urea disrupted hydrogen bonding in the drug lattice while SXS contributed hydrophobic and electrostatic interactions. Their combined action created a cooperative solubilizing environment that reduced crystallinity and improved molecular dispersion.

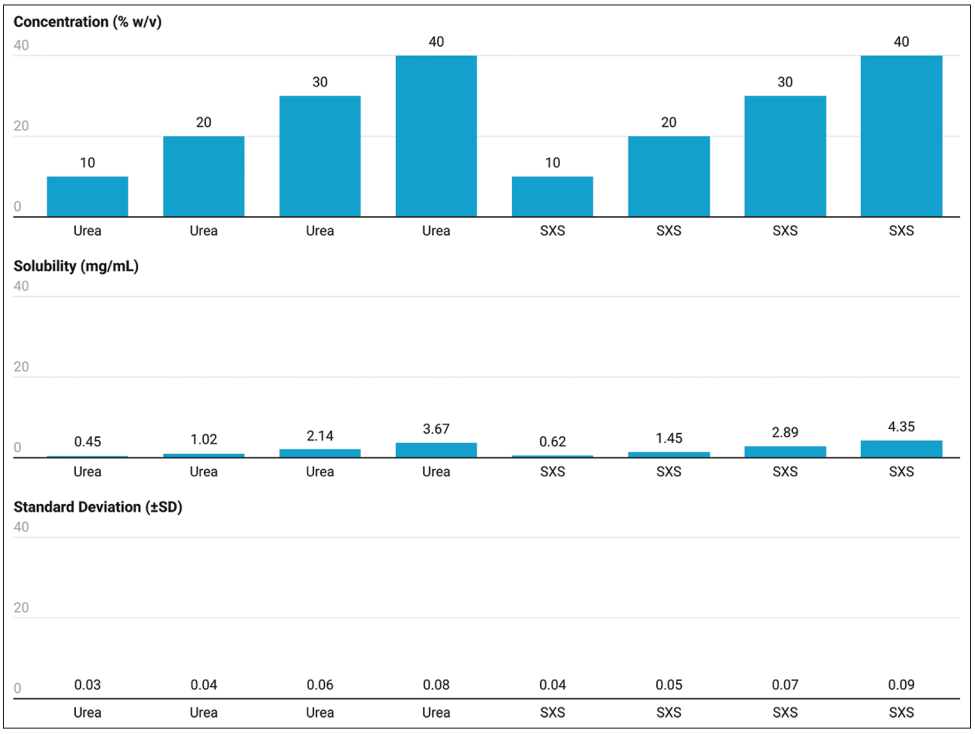

Figure 1: Equilibrium solubility of posaconazole in individual hydrotropic solutions

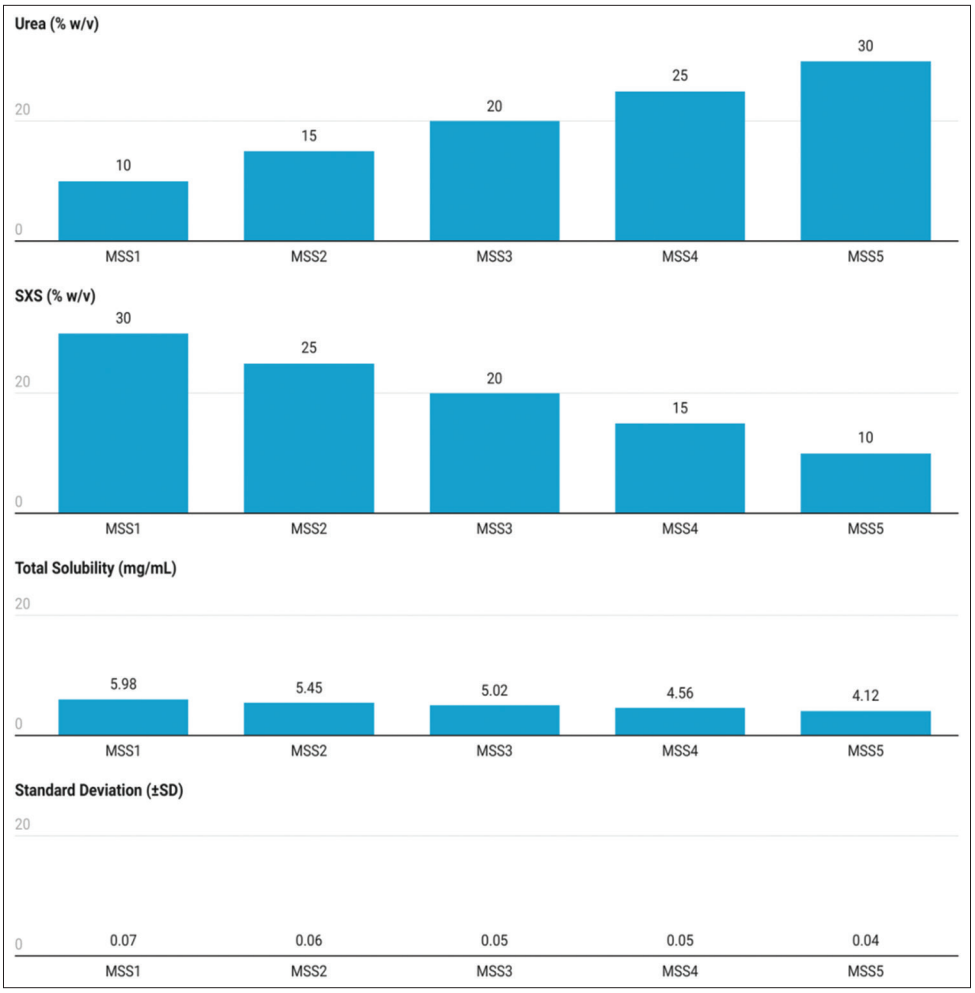

Figure 2: Equilibrium solubility of posaconazole in mixed solvency systems

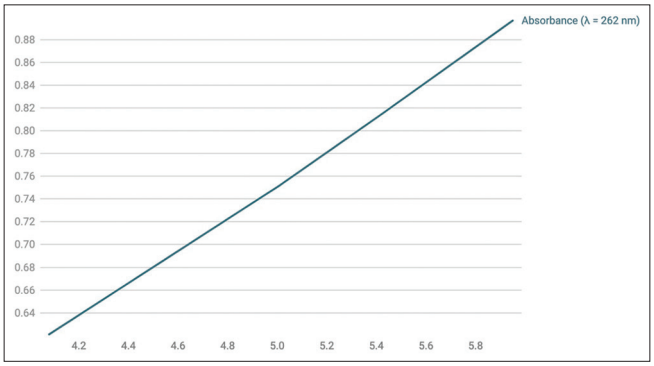

Figure 3: Calibration plot

Compatibility Analysis via FTIR

FTIR spectra showed all characteristic functional peaks of posaconazole intact in both mixtures and MSS3. Only minor shifts were observed, confirming no chemical interactions but possible weak physical interactions such as hydrogen bonding.

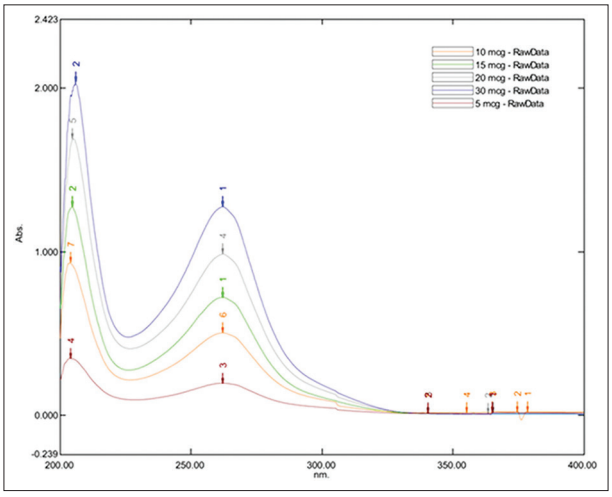

Figure 4: Ultraviolet spectrum of posaconazole at different hydrotropic and mixed solvency media

Thermal Analysis via DSC

DSC analysis revealed a slight reduction and broadening of the drug's melting point from

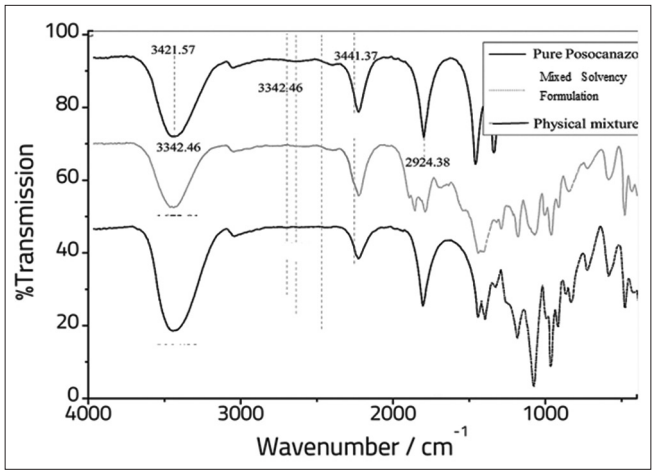

Figure 5: Fourier-transform infrared spectroscopy spectrum of posaconazole and the selected hydrotropic agents

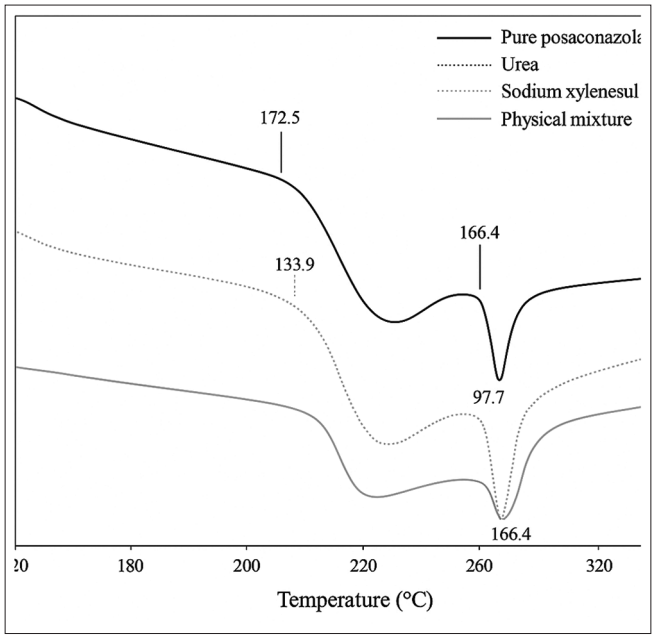

Figure 6: Differential scanning calorimetry graph of pure drug, physical mixture, and optimized formulation

170.25°C to 166.51°C in MSS3. This suggested partial amorphization and molecular dispersion, consistent with improved solubility. No evidence of chemical degradation was observed.

Stability Studies

MSS3 remained stable under accelerated conditions for 30 days. The formulation retained clarity, showed minimal pH variation (6.84–6.76), and maintained >98% drug content, indicating excellent physical and chemical stability.

Implications for Pharmaceutical Development

This MSS offers a safe, simple, and scalable method for solubility enhancement using pharmaceutically acceptable excipients. By avoiding complex processing, it provides a cost-effective strategy for posaconazole and potentially other poorly soluble drugs.

CONCLUSION

The study demonstrated the effectiveness of a mixed solvency approach using urea and SXS to enhance the solubility of posaconazole, a poorly water-soluble antifungal drug. Analytical evaluations (FTIR and DSC) confirmed no chemical incompatibility, with only minor physical interactions observed. Stability studies proved the optimized formulation (MSS3) retained clarity, pH, and >98% drug content over 30 days. Solubility improved significantly, reaching 6.98 mg/mL versus moderate increases with individual solubilizers. This safe, scalable strategy simplifies formulation, offering a promising solution for poorly soluble drugs.

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