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Artículos originales

Cocrystallization Driven Enhancement of Solubility and Dissolution Profile of Loteprednol Etabonate: A Strategy for Improved Biopharmaceutical Performance

Mejora de la Solubilidad y del Perfil de Disolución de Loteprednol Etabonate mediante Co-Cristalización: Una Estrategia para Potenciar el Rendimiento Biofarmacéutico

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Conflict of Interest

Authors declare no conflict of interest.

Author Contribution

VSA and PAD conceptualize, designed, and performed experiments and prepared the first draft of the manuscript. JPA and VPW rewrite the manuscript and performed DSC and FTIR. PKS and KKM performed literature survey and performed characterization on UV, PXRD & SEM. VSA and JPA supervised all work. All authors reviewed the manuscript.

Resumen

Antecedentes: El Loteprednol Etabonato, un fármaco de Clase II del Sistema de Clasificación Biofarmacéutica (BCS), presenta una baja solubilidad acuosa y una biodisponibilidad limitada, lo que dificulta su administración oral y eficacia terapéutica.

Objetivo: Mejorar la solubilidad y la velocidad de disolución del Loteprednol Etabonato mediante la formulación de co-cristales farmacéuticos con conformadores químicos seleccionados.

Métodos: Se prepararon co-cristales de Loteprednol Etabonato en proporciones estequiométricas con cafeína, ácido benzoico y ácido salicílico utilizando la técnica de evaporación del disolvente. Los co-cristales fueron caracterizados mediante espectroscopía infrarroja por transformada de Fourier (FTIR), calorimetría diferencial de barrido (DSC), difracción de rayos X en polvo (PXRD) y microscopía electrónica de barrido (SEM). Se realizaron estudios de solubilidad y disolución para evaluar el rendimiento biofarmacéutico.

Resultados: Todos los co-cristales mostraron una mejora en los perfiles de solubilidad y disolución en comparación con el fármaco puro. El co-cristal de Loteprednol-ácido salicílico presentó la mayor solubilidad, alcanzando 31.90 µg/ml. Las caracterizaciones confirmaron una co-cristalización exitosa, con evidencia de interacciones no covalentes, mayor cristalinidad y cambios morfológicos.

Conclusión: La co-cristalización farmacéutica mejoró significativamente la solubilidad y la velocidad de disolución del Loteprednol Etabonato. Esta estrategia representa un enfoque prometedor para mejorar las propiedades biofarmacéuticas de fármacos con baja solubilidad en agua sin alterar su estructura química.

Palabras clave: Loteprednol Etabonato, co-cristalización, mejora de la solubilidad, Clase II BCS, ácido salicílico, PXRD, velocidad de disolución.

Abstract

Background: Loteprednol Etabonate, a BCS Class II drug, suffers from poor aqueous solubility and limited bioavailability, posing challenges in its oral drug delivery and therapeutic efficacy.

Objective: To enhance the solubility and dissolution rate of Loteprednol Etabonate through the formulation of pharmaceutical cocrystals with selected conformers.

Methods: Cocrystals of Loteprednol Etabonate were prepared using equimolar ratios with caffeine, benzoic acid, and salicylic acid via the solvent evaporation technique. The cocrystals were characterized using Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Powder X-ray Diffraction (PXRD), and Scanning Electron Microscopy (SEM). Solubility and dissolution studies were conducted to assess biopharmaceutical performance.

Results: All cocrystals showed improved solubility and dissolution profiles compared to the pure drug. The Loteprednol-salicylic acid cocrystal exhibited the highest solubility of 31.90 µg/ml. Characterization confirmed successful cocrystallization, with evidence of non-covalent interactions, enhanced crystallinity, and morphological changes.

Conclusion: Pharmaceutical cocrystallization significantly improved the solubility and dissolution rate of Loteprednol Etabonate. This strategy offers a promising approach to enhance the biopharmaceutical properties of poorly water-soluble drugs without altering their chemical structure.

KEYWORDS: Loteprednol Etabonate, cocrystallization, solubility enhancement, BCS Class II, salicylic acid, PXRD, dissolution rate.

Highlights

Loteprednol Etabonate (LE) is a BCS Class II drug with poor aqueous solubility and limited oral bioavailability.

- Cocrystal formation was employed to enhance solubility and dissolution of LE. Cocrystals were prepared with caffeine, benzoic acid, and salicylic acid (1:1 molar ratio) using solvent evaporation.
- FTIR, DSC, PXRD, and SEM analyses confirmed successful cocrystal formation with distinct structural and morphological changes. All cocrystals exhibited improved solubility; LE-salicylic acid cocrystal showed the highest solubility (31.90 µg/ml).

Dissolution studies revealed significant enhancement in drug release compared to pure LE. Cocrystallization proved to be a simple, scalable, and effective strategy to enhance solubility and biopharmaceutical performance without altering drug structure.

Introduction

Loteprednol etabonate (LE) is a corticosteroid widely prescribed for the treatment of ophthalmic inflammatory conditions, such as allergic conjunctivitis, anterior uveitis, and post-operative inflammation following ocular surgeries⁽¹⁾. It is a retro metabolically designed drug with a unique ester-based structure, aimed at minimizing the side effects associated with traditional corticosteroids^(2,3). Despite its therapeutic potential and favorable safety profile, LE is classified under the Biopharmaceutics Classification System (BCS) as a Class II drug, characterized by poor water solubility and high permeability⁽⁴⁾. This intrinsic low aqueous solubility significantly limits its dissolution rate and, consequently, its bioavailability, especially in ocular drug delivery applications where rapid onset of action and optimal therapeutic concentrations are crucial^(5,6).

Improving the solubility and dissolution profile of poorly soluble drugs like LE remains a formidable challenge in pharmaceutical formulation. Conventional approaches such as micronation, solid dispersions, and the use of solubilizing agents have been explored extensively, yet often these strategies fall short in achieving sustained enhancement in solubility without compromising drug stability or manufacturability. In recent years, cocrystallization has emerged as a promising alternative technique to address solubility issues of poorly water-soluble drugs. Cocrystals are crystalline materials composed of the active pharmaceutical ingredient (API) and one or more conformers, bound together by non-covalent interactions such as hydrogen bonding, π - π stacking, or van der Waals forces. Unlike salts or polymorphs, cocrystals do not alter the covalent structure of the drug molecule but can significantly modify its physicochemical properties, including solubility, dissolution rate, stability, and mechanical behavior⁽⁷⁻¹⁰⁾.

The rationale behind employing cocrystallization lies in the ability to fine tune the drug's solubility and dissolution characteristics without the need for chemical modification. The success of this approach largely depends on the selection of suitable conformers that are GRAS (Generally Recognized As Safe) and capable of forming stable supramolecular synthons with the drug molecule. Several studies have demonstrated the effectiveness of pharmaceutical cocrystals in enhancing the solubility and bioavailability of BCS Class II and IV drugs, thereby improving their therapeutic efficacy⁽¹¹⁻¹³⁾.

In the context of LE, cocrystallization presents an innovative and rational strategy to overcome its solubility limitations. However, limited research has been reported on the application of this technique to LE, particularly in identifying appropriate conformers and optimizing the crystallization process to yield pharmaceutically acceptable solid forms with improved dissolution behavior⁽¹⁴⁻¹⁶⁾.

Therefore, the present study aims to enhance the solubility and dissolution rate of Loteprednol etabonate through cocrystallization using a systematic approach. The study involves the selection of suitable conformers based on literature survey, experimental screening using solvent evaporation method, followed by characterization of the synthesized cocrystals using a range of analytical techniques, including Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR), Powder X-ray Diffraction (PXRD), and Scanning Electron Microscopy (SEM). Furthermore, the solubility and dissolution profiles of the developed cocrystals are evaluated and compared with that of the pure drug⁽¹⁷⁻¹⁹⁾.

This research is anticipated to provide valuable insights into the feasibility and advantages of cocrystallization in modifying the dissolution behavior of LE, potentially paving the way for the development of improved ophthalmic formulations with enhanced therapeutic performance.

Materials and reagents

Loteprednol Etabonate (LE): Pharmaceutical grade Loteprednol Etabonate was procured as a gift sample from a reputed pharmaceutical manufacturer in India.

Conformers: The conformers used for cocrystallization were selected based on GRAS status and the literature review. Conformers included caffeine, benzoic acid and salicylic acid (Merck analytical grade).

Solvents: Analytical grade solvents such as methanol, ethanol, acetone, and distilled water were used throughout the experiments.

All chemicals and reagents were of analytical grade and used without further purification.

Methodology

Preparation of Cocrystals

Take the equimolar amount of Loteprednol Etabonate and conformer in 1:1 ratio, the required quantities of Loteprednol Etabonate and conformer were calculated based on their respective molecular weights. Transfer both to a 100 mL beaker and add 15 mL of methanol to dissolve it. Then stir the mixture at 40-50 °C on Hot Plate and stirrer until a clear solution is achieved (it takes about 30 minutes). After complete evaporation, collect the solid crystals and store in air tight container.

Characterization of Cocrystals

1. Fourier Transform Infrared Spectroscopy (FTIR)

The produced cocrystals' potential intermolecular interactions between Loteprednol Etabonate and specific conformers (caffeine, salicylic acid, and benzoic acid) were characterized using FTIR analysis. Using an FTIR spectrophotometer, samples such as synthesized cocrystals and pure Loteprednol Etabonate were examined. To guarantee proper contact, a little amount of solid sample was put directly onto the surface and uniform pressure was applied using the pressure arm. The spectra were acquired in the range of 4000 to 400 cm^{-1} . To improve accuracy, 16 scans were performed per sample. Loteprednol Etabonate typical functional group peaks, such as N-H stretching, C=O stretching, aromatic C=C, and sulphonamide sulfonamide (S=O) vibrations, were closely examined and compared to those of cocrystals. Shifts in peak locations or intensity were utilized to infer hydrogen bonding or other non-covalent interactions, validating cocrystal formation.

2. Differential Scanning Calorimetry (DSC)

To evaluate the thermal behavior and possible interactions between Loteprednol Etabonate and conformers in the produced cocrystals, Differential Scanning Calorimetry (DSC) was used. A differential scanning calorimeter was used to perform the DSC analysis. Synthesized cocrystals and 2-5 mg of pure Loteprednol Etabonate samples that had been precisely weighed were placed in standard aluminum pans. The reference was an empty, sealed aluminum pan. To prevent oxidative degradation, the samples were heated from 30°C to 300°C at a rate of 10°C per minute in a nitrogen environment operating at 20-50 ml/min. The Thermogram has been studied for endothermic peaks, onset temperatures, and enthalpy changes (ΔH). The modification or removal of the drug or conformer's melting peak, followed by the development of a new peak at a different temperature, was interpreted as evidence of cocrystal formation, signifying probable molecular interaction and altered crystal structure.

3. Powder X-ray Diffraction (PXRD)

Powder X-Ray Diffraction (PXRD) was used to study the crystalline nature and structural changes in Loteprednol Etabonate after cocrystal formation with various conformers. The PXRD patterns of pure Loteprednol Etabonate and produced cocrystals were recorded with an X-ray diffractometer. The investigation was conducted at room temperature using Cu-K α radiation ($\lambda = 1.5406 \text{ \AA}$) at a voltage of 40 kV and current of 40 mA. Each sample was gently ground to a consistent powder and placed on the sample

holder, which ensured a flat and level surface. The diffraction data were acquired across a 2θ range of 5° to 50° , with a step size of 0.02° and a scanning rate of 2° per minute. The obtained diffractograms were examined to determine the existence of sharp peaks indicating crystalline formations. Cocrystal production was confirmed by comparing peak locations and intensities of pure drug and cocrystals. The emergence of new peaks, the elimination of typical peaks, or changes in peak intensity and position all indicated the production of a new crystalline phase separate from the pure components, proving successful cocrystallization.

4. Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) was used to analyze the surface morphology and particle shape of Loteprednol Etabonate and its synthesized cocrystals. The analysis was carried out using a scanning electron microscope with an accelerating voltage of 15-20 kV. A small amount of each finely powdered sample was placed on a double-sided carbon adhesive tape attached to an aluminum SEM stub. The excess, loose particles were gently removed to allow for clear imaging of the sample surface. To improve conductivity and prevent charging under the electron beam, the samples were coated with a thin layer of gold or platinum using a sputter coater for about 60-120 seconds. The coated samples were then transferred to the SEM apparatus and photographed under vacuum. Micrographs were taken at various magnifications to study surface properties, particle size, and crystal habits. The shape of cocrystals was compared to pure drugs and physical combinations. Distinct changes in shape, size, and surface roughness in the cocrystals were interpreted as evidence of successful cocrystallization and creation of a new solid phase.

5. Solubility Studies

The solubility of Loteprednol Etabonate and its cocrystal was studied in methanol. The excess cocrystal (100mg) was transferred to a glass stopper containing 50 ml of medium and stirred at $37 \pm 0.5^\circ\text{C}$ for 1 hour on a magnetic stirrer set to 150 rpm. UV spectrophotometry at 242 nm was used to determine the appropriate dilution and concentration.

6. Dissolution Studies

Dissolution tests were performed using a USP Type II (paddle) dissolution apparatus. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8, maintained at $37 \pm 0.5^\circ\text{C}$ and stirred at 50 rpm. An amount equivalent to 10 mg of LE (either pure or cocrystal form) was added to the medium. Aliquots (5 mL) were withdrawn at predetermined intervals (10, 20, 30, 40, 50 and 60 minutes), filtered, and analyzed spectrophotometrically at 242 nm. The withdrawn volume was replaced with fresh buffer each time.

Results and Discussion

1. Cocrystal Formation

The conformers selected as Caffeine, Benzoic acid and salicylic acid; were screened for their ability to form stable cocrystals with Loteprednol Etabonate (LE) using solvent evaporation method. Among these, LE-Benzoic acid and LE-salicylic acid combinations produced consistent, crystalline solid products, while LE-caffeine yielded a partially crystalline form. Cocrystal formation was indicated visually by the change in crystal habit and further confirmed by solid-state characterization techniques.

2. Fourier Transform Infrared Spectroscopy (FTIR)

The spectrum of Loteprednol etabonate pure shows characteristic peaks around 3325 cm^{-1} and 1653 cm^{-1} , indicative of O-H and C=O stretching vibrations typical of corticosteroids. Similarly, the spectrum of Caffeine exhibits notable N-H stretching near 3721 cm^{-1} and alkyl vibrations around 2970 cm^{-1} , confirming the presence of methylated nitrogen groups. The Benzoic Acid spectrum displays strong peaks at approximately 3515 cm^{-1} and 1656 cm^{-1} , characteristic of carboxylic acid functionalities. In the case

of Salicylic Acid, peaks near 3731 cm⁻¹ are attributed to phenolic O-H groups, along with aromatic ring vibrations close to 1600 cm⁻¹, confirming the phenolic and ester components. A comparative analysis of these spectra suggests overlapping peaks, particularly in mixture samples, indicating possible interactions or coexistence of multiple active ingredients. Variations in peak intensity and position across the spectra support the presence of modifications, impurities, or composite formation within the formulations. Overall, the spectral data confirm the identities of the compounds and demonstrate the efficacy of FTIR spectroscopy as a rapid qualitative tool for pharmaceutical analysis, with the spectra in providing clear evidence of functional groups and molecular integrity in each sample. The FTIR spectra of the LE-Salicylic acid cocrystal as shown in figure 1 reveal distinctive features corresponding to their respective chemical structures and functional groups.

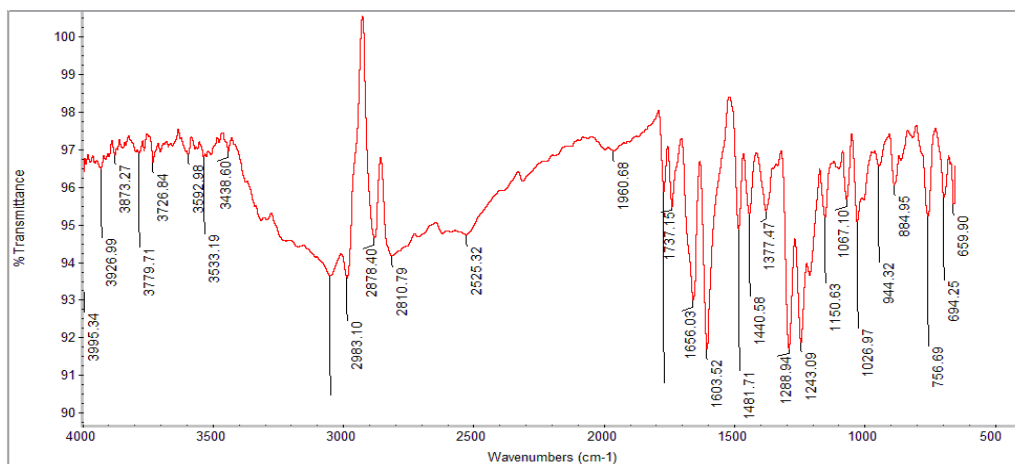


Figure 1. FTIR spectra of Loteprednol etabonate-Salicylic acid cocrystals

3. Differential Scanning Calorimetry (DSC)

The DSC (Differential Scanning Calorimetry) analysis was used to compare the thermal behavior of Loteprednol Etabonate, Salicylic Acid, Caffeine, and Benzoic Acid. Loteprednol Etabonate showed a single, sharp melting point with an onset at 238.67 °C, peak at 241.14 °C, and end set at 243.41 °C, which indicates that the sample is pure, crystalline, and thermally stable. LE-Salicylic Acid showed peak at 134.37 °C, which may suggest the presence of one form. LE-Caffeine had one clear melting point 198.10 °C, showing good purity and stability. LE-Benzoic Acid also showed endotherm at higher temperature around 239.65 °C, which could indicate melting followed by some degradation. The absence of individual melting peaks of LE or conformers in the cocrystal thermograms confirmed the formation of a new crystalline phase, not a mere physical blend, as shown in figure 2.

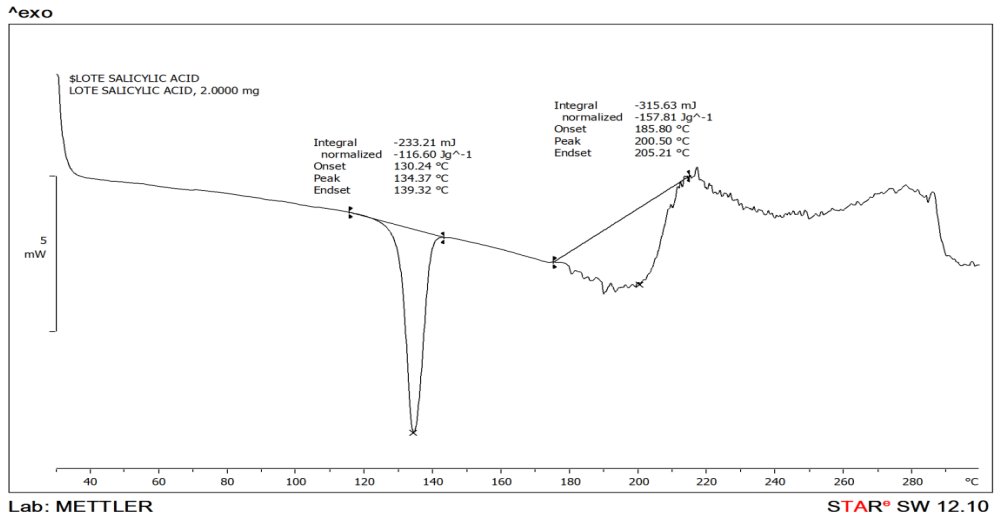


Figure 2. DSC thermogram of Loteprednol etabonate-Salicylic acid cocrystals

4. Powder X-ray Diffraction (PXRD)

The X-ray diffraction (XRD) as in figure 3, shows clear differences between the pure LE and cocrystals along with conformers. PXRD patterns of pure LE demonstrated characteristic intense peaks at 2θ values of 15.97°, 16.66°, 18.5° and 21.70°, corresponding to its crystalline lattice. New and unique peaks were observed in the LE-Caffeine, LE-Benzoic acid and LE-Salicylic acid cocrystals: LE- Caffeine: New Peaks at 11.51°, 16.77°, and 24.06°

LE- Benzoic acid: New Peaks with good intensities at 12.50°, 15.77°, 19.11°, and 20.19°.

LE-Salicylic acid: New Peaks with good intensities at 10.78°, 11.99°, 17.08°, and 18.80°

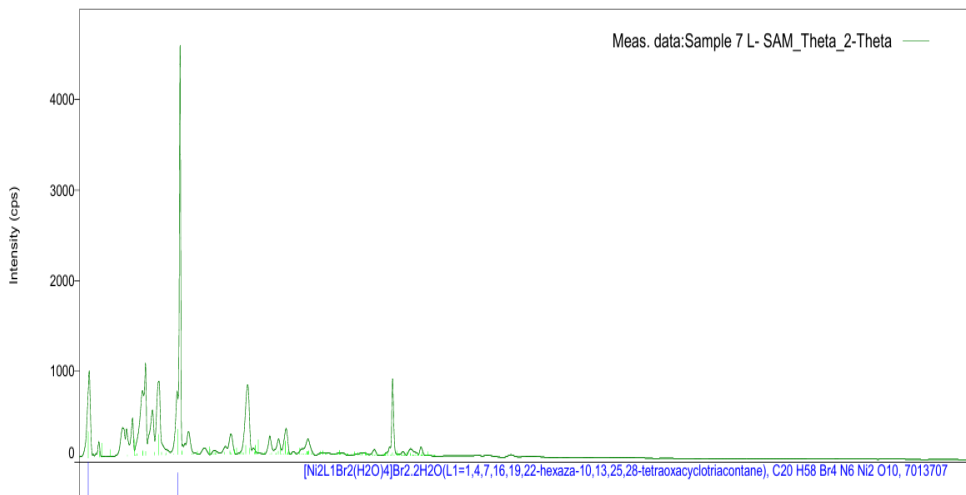


Figure 3. PXRD of Loteprednol etabonate-Salicylic acid cocrystals

Figure 3 PXRD showed disappearance of original LE peaks and emergence of novel diffraction patterns confirming new polymorphic forms via PXRD index matching. These findings validate successful cocrystal formation and distinguish the products from their parent compounds.

5. Scanning Electron Microscopy (SEM)

The SEM images revealed significant changes in surface morphology. Loteprednol Etabonate pure reveals a highly porous and loosely packed structure, which is advantageous for applications requiring a high surface area, such as catalysis or adsorption, and suggests a carefully controlled synthesis process. In contrast, L.E-Caffeine crystalline, plate-like formations likely resulting from post-treatment crystallization; these structures may improve mechanical strength but could reduce the overall surface area. L.E-Benzoic Acid presents rough, irregular flakes, indicative of partial recrystallization or mechanical grinding, offering a potential balance between surface area and structural stability. L.E-Salicylic Acid displays fine particles coating larger ones, characteristic of a composite material system that enhances active surface sites while maintaining the bulk properties of the substrate. Together, these varied morphologies highlight how processing conditions influence material structure and, consequently, their functional performance. SEM image confirmed morphological transformation into a visual indicator of new solid-state properties associated with cocrystallization as shown in Figure 4.

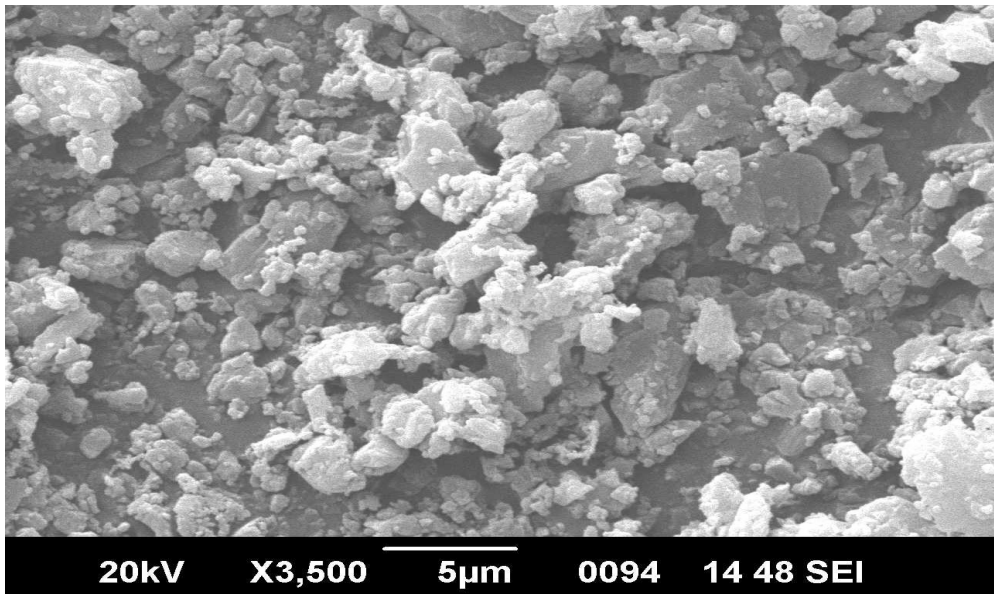


Figure 4. SEM image of Loteprednol etabonate-Salicylic acid cocrystals

6. Solubility Studies

The solubility of Loteprednol Etabonate and its cocrystals was evaluated using UV spectrophotometry. Pure Loteprednol Etabonate exhibited a solubility of 12.29 µg/ml. Upon formation of cocrystals with various conformers, a marked improvement in solubility was observed. The Loteprednol Etabonate-Caffeine cocrystal showed a solubility of 19.05 µg/ml, while the benzoic acid cocrystal exhibited 23.78 µg/ml. The highest enhancement was observed with salicylic acid, where the solubility increased to 31.90 µg/ml. These results suggest that cocrystallization is a promising approach to improve the aqueous solubility of poorly soluble drugs like Loteprednol Etabonate. Bar graph showing more than two-fold increase in solubility for LE-Salicylic acid cocrystals as in figure 5.

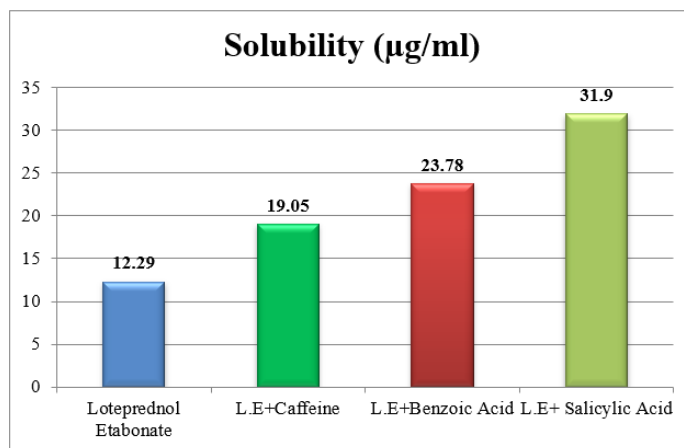


Figure 5. Solubility Chart for Loteprednol Etabonate and Cocrystals

7. Dissolution Studies

The dissolution profiles of pure Loteprednol Etabonate and its cocrystals with caffeine, benzoic acid, and salicylic acid were evaluated over a 60 min period under standardized conditions (900 mL dissolution medium, $37 \pm 0.5^\circ\text{C}$, paddle rotation at 50 rpm). The concentration of dissolved drug was measured at fixed time intervals to compare the dissolution behavior of the pure drug versus its cocrystals. The results as in table 1 indicate a significant enhancement in the dissolution rate of Loteprednol Etabonate when formulated as cocrystals with all three conformers. At every time point, the amount of drug dissolved from the cocrystal formulations was notably higher than that from the pure drug. Among the conformers tested, the cocrystal with salicylic acid exhibited the highest dissolution, followed closely by the cocrystals with benzoic acid and caffeine as shown in figure 6.

Table 1. Dissolution Study of Loteprednol Etabonate and Cocrystals

Time (min)	Pure Loteprednol Etabonate (µg/ml)	Loteprednol Etabonate + Caffeine (µg/ml)	Loteprednol Etabonate + Benzoic Acid (µg/ml)	Loteprednol Etabonate + Salicylic Acid (µg/ml)
10	7.2	11.1	12.4	14.9
20	11.3	18.5	20.8	23.4
30	16.7	24.6	28.7	31.5
40	19.8	29.4	33.5	37.8
50	22.6	32.7	37.9	42.1
60	25.4	34.5	40.2	46

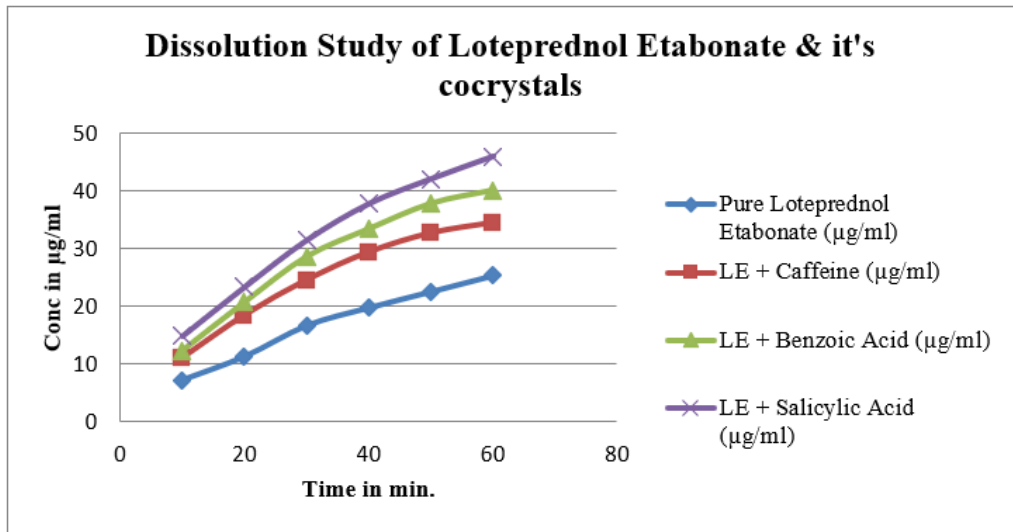


Figure 6. Dissolution study of Loteprednol Etabonate and it's cocrystals

The faster dissolution is likely due to the improved surface area, faster wetting, and reduced crystal lattice energy of cocrystals. This study demonstrates the successful application of cocrystallization to overcome the solubility limited bioavailability of Loteprednol Etabonate. Through rational conformer selection, optimized crystallization methods, and comprehensive characterization, novel LE cocrystals particularly with salicylic acid exhibited superior aqueous solubility and enhanced dissolution rate. These findings are consistent with literature reports on other BCS Class II drugs and reinforce the utility of cocrystals as a powerful strategy in modern pharmaceutical development. Future work could include *in vivo* pharmacokinetic studies, stability analysis, and formulation into ophthalmic dosage forms to translate these benefits into therapeutic gains.

Conclusion

This study demonstrates that cocrystallization is a viable approach to improve the solubility, dissolution, and permeability of Loteprednol Etabonate (LE). The LE–salicylic acid cocrystal showed the greatest enhancement, with nearly two-fold increases in solubility and dissolution compared to the pure drug. PXRD confirmed the formation of a distinct crystalline form, while UV spectroscopy ensured analytical reliability. Overall, the improved physicochemical and biopharmaceutical properties highlight cocrystallization as a robust and scalable strategy for LE development, consistent with reported successes for other poorly soluble drugs.

Declaration

Ethics approval and consent to participate

We strictly adhered to ethical guidelines in conducting this research, ensuring no animals or humans were involved.

Clinical Trails:

Not Applicable

Consent to publish declaration:

Not Applicable

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