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Original Article

Enhancing Ezetimibe Absorption: Formation and Characterisation of Drug Cocrystals with Carboxylic Acid Coformers

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Abstract

Background: Ezetimibe (EZT) is a newer FDA-approved drug that inhibits cholesterol absorption in the intestines without affecting the uptake of fat-soluble vitamins. However, EZT is classified under the Biopharmaceutics Classification System (BCS) as a Class II drug, characterised by low solubility and limited absorption. **Objective:** This study aims to enhance the solubility and bioavailability of EZT through cocrystallisation with carboxylic acid coformers. **Methods:** Cocrystals were prepared using the solvent-drop grinding technique. Characterisation was performed using Particle Size Analysis (PSA), Powder X-ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscopy (SEM), and dissolution testing. **Results:** The EZT cocrystals exhibited a smaller particle size (0.728 µm) compared to pure EZT (1.049 µm), and PXRD analysis confirmed the formation of a new crystalline phase. DSC results showed a reduced melting point for the cocrystal (76.99°C) compared to pure EZT (81.54°C), while FTIR spectra indicated the formation of hydrogen bonds. SEM images revealed that the cocrystals had a more fragmented and rougher morphology compared to the smoother particles of pure EZT. Dissolution testing demonstrated enhanced solubility, with 49.13% of the EZT cocrystal dissolved at 15 minutes versus 13.90% for pure EZT, indicating improved potential for absorption and therapeutic efficacy. **Conclusion:** The formation of EZT cocrystals significantly enhances the drug's solubility and absorption, supporting the potential of cocrystallisation as an effective strategy for improving the bioavailability of poorly soluble drugs.

Keywords: *Absorption; Cholesterol; Ezetimibe Co-Crystal; Solvent Drop Grinding Ezetimibe*

Introduction

Diseases associated with elevated cholesterol levels, including high concentrations of triglycerides and Low-Density Lipoprotein (LDL) cholesterol, are among the leading causes of mortality in Indonesia. These conditions can lead to various health problems, such as hypercholesterolemia, hyperlipidaemia, coronary artery disease, hypertension, and stroke (Aris *et al*., 2024). Currently, cholesterol management in the general population relies heavily on medications from the statin class, such as atorvastatin, simvastatin, fenofibrate, gemfibrozil, and ezetimibe. These medications are typically administered orally, as the oral route remains the most common and convenient method of drug delivery. However, statins are known to cause several side effects, the most notable being rhabdomyolysis. Additionally, statin use has been linked to reversible memory impairment in patients over the age of 50, which typically resolves upon discontinuation of the therapy (Yang *et al*., 2022).

Ezetimibe (EZT) is a relatively new class of cholesterol-lowering medication approved by the Food and Drug Administration (FDA). It functions by selectively inhibiting the absorption of dietary and biliary cholesterol in the small intestine without interfering with the absorption of fat-soluble vitamins. Ezetimibe

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is classified under the Biopharmaceutics Classification System (BCS) as a class II drug, characterised by low aqueous solubility and consequently a slow dissolution rate and incomplete intestinal absorption. Therefore, the development of innovative cocrystallisation techniques is necessary to enhance its dissolution profile and improve bioavailability (Ferdiansyah *et al*., 2021).

A cocrystal is a crystalline material composed of two or more different molecular species that form a new solid phase through non-covalent interactions. In pharmaceutical science, cocrystals are considered molecular or supramolecular complexes (Ancheria *et al*., 2019). Moreover, the additional molecule used in cocrystal formation is known as a coformer, which plays a key role in enhancing the solubility of the active pharmaceutical ingredient. Improved solubility typically correlates with increased bioavailability of the drug (Ferdiansyah *et al*., 2021).

An ideal coformer must possess specific characteristics: it should be non-toxic, pharmacologically inert, water-soluble, capable of forming non-covalent bonds (especially hydrogen bonds), chemically compatible with the active compound, and not form irreversible complexes. Furthermore, coformer selection is restricted to substances listed or approved by regulatory bodies such as the FDA. Common coformers used in pharmaceutical cocrystallisation include carbohydrates (e.g., saccharin), carboxylic acids (e.g., fumaric, succinic, tartaric acids), alcohols, amides, and amino acids (Singh *et al*., 2023).

In this study, a carboxylic acid derivative was selected as the coformer for cocrystal development. These compounds are capable of acting as hydrogen bond donors or acceptors with acidic, basic, or neutral drug molecules, facilitating cocrystal formation (Alatas *et al*., 2020). Many carboxylic acid coformers are recognised as Generally Recognized as Safe (GRAS) by the FDA. Examples include phosphodiesterase-4 inhibitor in chlorbipram cocrystals (Zhou *et al*., 2020), oxalic acid used in apixaban cocrystals (Asati *et al*., 2023), gallic acid in metronidazole cocrystals (Dyba *et al*., 2023), gallic acid in metronidazole cocrystals (Dyba *et al*., 2023), and gentisic acid in chlorpromazine cocrystals (Li *et al*., 2023).

Furthermore, the relevance of this study lies in its contribution to solving one of the major limitations in the oral delivery of Ezetimibe—its poor aqueous solubility. As a BCS Class II drug, Ezetimibe's therapeutic effectiveness is often constrained by its limited dissolution in gastrointestinal fluids, leading to suboptimal absorption and bioavailability. By developing a cocrystal formulation using pharmaceutically acceptable coformers, this research offers a promising approach to overcoming solubility barriers without altering the drug’s pharmacological structure. The significance of this study extends beyond Ezetimibe alone; it provides a framework for enhancing the performance of other poorly soluble drugs using green and scalable solid-state modification strategies. Moreover, with cardiovascular diseases remaining a leading cause of death globally and particularly in Indonesia, the formulation of more efficient cholesterol-lowering drugs holds substantial public health importance. This work supports the growing shift toward rational crystal engineering in drug formulation and could lead to more effective, safer, and patient-friendly dosage forms in the future.

Materials and Methods

Tools and Materials

The instruments used include UV-Vis Spectrophotometer (SHIMADZU UV-1800), Particle Size Analyser/PSA (Malvern Mastersizer), X-Ray Diffractometry/XRD (RIGAKU Mini FlexII), Differential Scanning Calorimetry/DSC (Perkin Elmer DSC 4000), Fourier Transform Infrared/FTIR (SHIMADZU IR Prestige), and Scanning Electron Microscope/SEM (Hitachi TM 3000). The materials used are EZT (Infalabs-BPOM), methanol (PT Bratachem), carboxylic acid (PT Bratachem), distilled water (PT Bratachem), NaOH (PT Bratachem), and KH2PO4. (PT Bratachem).

Preparation of Ezetimibe Cocrystals by Solvent-drop Grinding (SDG) technique

Ezetimibe and carboxylic acid were weighed in a 1:1 molar ratio and placed into a mortar. The mixture was ground manually for 15 minutes to ensure a homogenous blend. Subsequently, the ground mixture was transferred to an evaporating dish, and 5 mL of methanol p.a. was added. The mixture was then

left to dry at room temperature for 24 hours. After drying, the resulting powder was subjected to further characterisation.

Particle Size Analyzer (PSA)

The particle size of the microcapsules from the optimal formulation was analysed using a Malvern Mastersizer Particle Size Analyzer (Malvern Instruments). Measurements were conducted in a liquid medium using the Dynamic Light Scattering (DLS) method. The analysis was performed at a temperature of 25 °C with a measurement time of 70 seconds (Jia *et al*., 2023).

Powder X-Ray Diffraction (PXRD)

Powder X-Ray Diffraction (PXRD) patterns were recorded at room temperature using a Philip X'Pert diffractometer system. The Cu-Kα radiation source (λ = 1.54060 Å) was employed, and the instrument was operated at a voltage of 45 kV and a current of 40 mA. Diffraction data were collected by continuous scanning over a 2θ angle range of 5° to 50° (Aris*et al*., 2024).

Differential Scanning Calorimetry (DSC)

The thermal behavior of the samples was evaluated using a Perkin Elmer DSC 4000 instrument. Prior to analysis, the equipment was calibrated for temperature and heat flow accuracy using indium as a standard. Approximately 2–3 mg of the sample was weighed into an airtight aluminum pan. The sample was scanned over a temperature range of 50–250 °C at a heating rate of 10°C/min in a nitrogen atmosphere (flow rate 50 mL/min) (Torquetti *et al*., 2022).

Fourier Transform Infrared Spectroscopy (FTIR)

Fourier Transform Infrared Spectroscopy (FTIR) analysis was carried out using a Shimadzu IR Prestige spectrophotometer. Spectra were recorded in the range of 4000–500 cm^{-1} at a resolution of 4 cm^{-1} (Purwanto, Muthaharah & Andika, 2024).

Scanning Electron Microscopy (SEM)

The morphology and surface structure of the samples were examined using a Hitachi TM 3000 Scanning Electron Microscope. Approximately 10 mg of the sample was mounted on a specimen holder using double-sided adhesive tape and then sputter-coated with platinum for 10 seconds using a Hitachi E-1045 sputter coater. The sample was then placed in the microscope's chamber and observed at an accelerating voltage of 15 kV (Purwanto, Muthaharah & Andika, 2024).

Dissolution Test

Dissolution studies were conducted using a paddle-type dissolution tester. A sample containing the equivalent of 50 mg of Ezetimibe was introduced into 900 mL of phosphate buffer solution (pH 6.8) maintained at 37 ± 0.5°C. The solution was stirred at a constant speed of 100 rpm. At predetermined intervals (0, 5, 10, 15, 30, 45, 60, and 90 minutes), 5 mL of the dissolution medium was withdrawn and immediately replaced with an equal volume of fresh medium to maintain sink conditions. The absorbance of each sample was measured using UV-Visible spectrophotometry, and the concentration of Ezetimibe in both the pure form and cocrystal form was calculated (Purwanto, Muthaharah & Andika, 2024).

Results

The particle size of pure EZT is approximately 1.049 µm (Figure 1a). In contrast, the EZT cocrystal exhibits a reduced particle size of around 0.782 µm (Figure 1b), indicating improved dispersion after co-crystallisation.

Particle Size Analyzer (PSA)

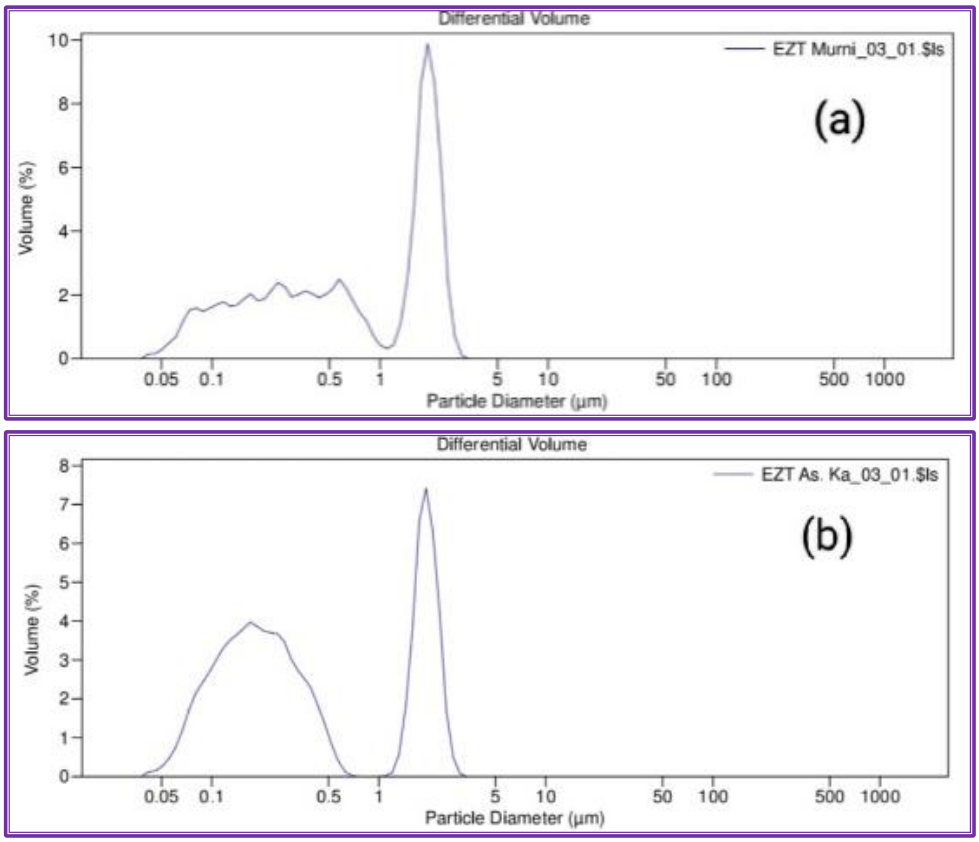

Figure 1: *Particle Size Distribution: (a) Pure Ezetimibe (EZT); (b) Ezetimibe (EZT) Cocrystal*

Powder X-Ray Diffraction (PXRD)

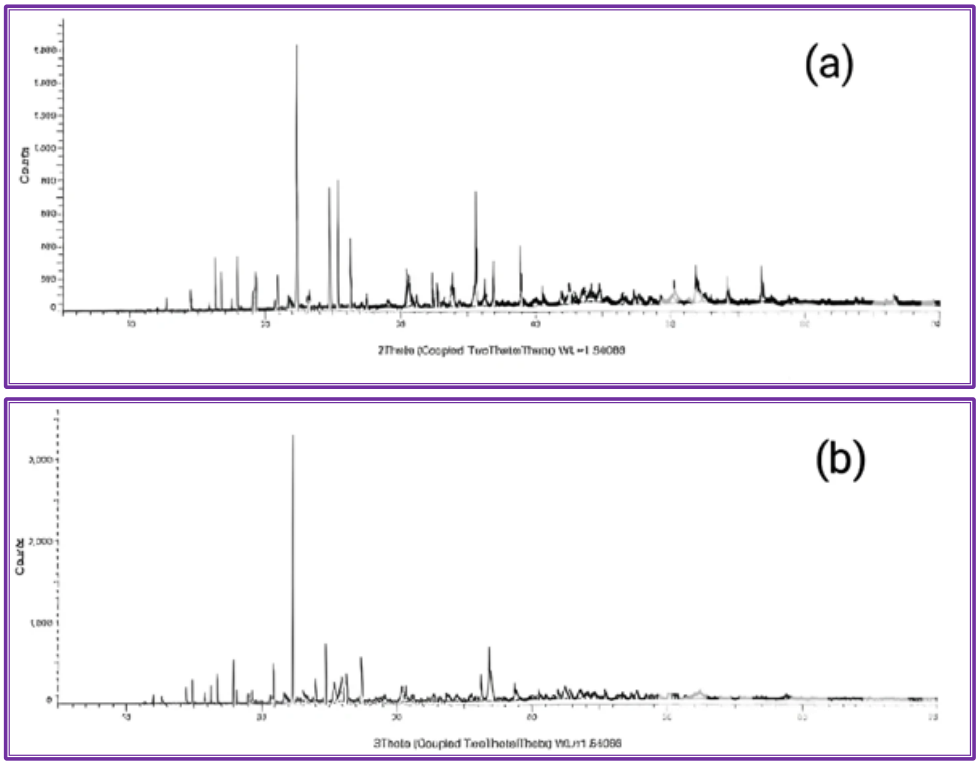

Figure 2: *PXRD Patterns: (a) Pure Ezetimibe (EZT); (b) Ezetimibe (EZT) Cocrystal*

Figure 2 displays changes in the X-ray diffraction patterns between pure EZT and its cocrystal. Pure EZT shows distinct peaks at 2θ = 22° (intensity: 1650) and 35° (intensity: 750), while the EZT cocrystal exhibits altered peak intensities—3300 at 22° and 100 at 35°—suggesting changes in crystallinity.

Differential Scanning Calorimetry (DSC)

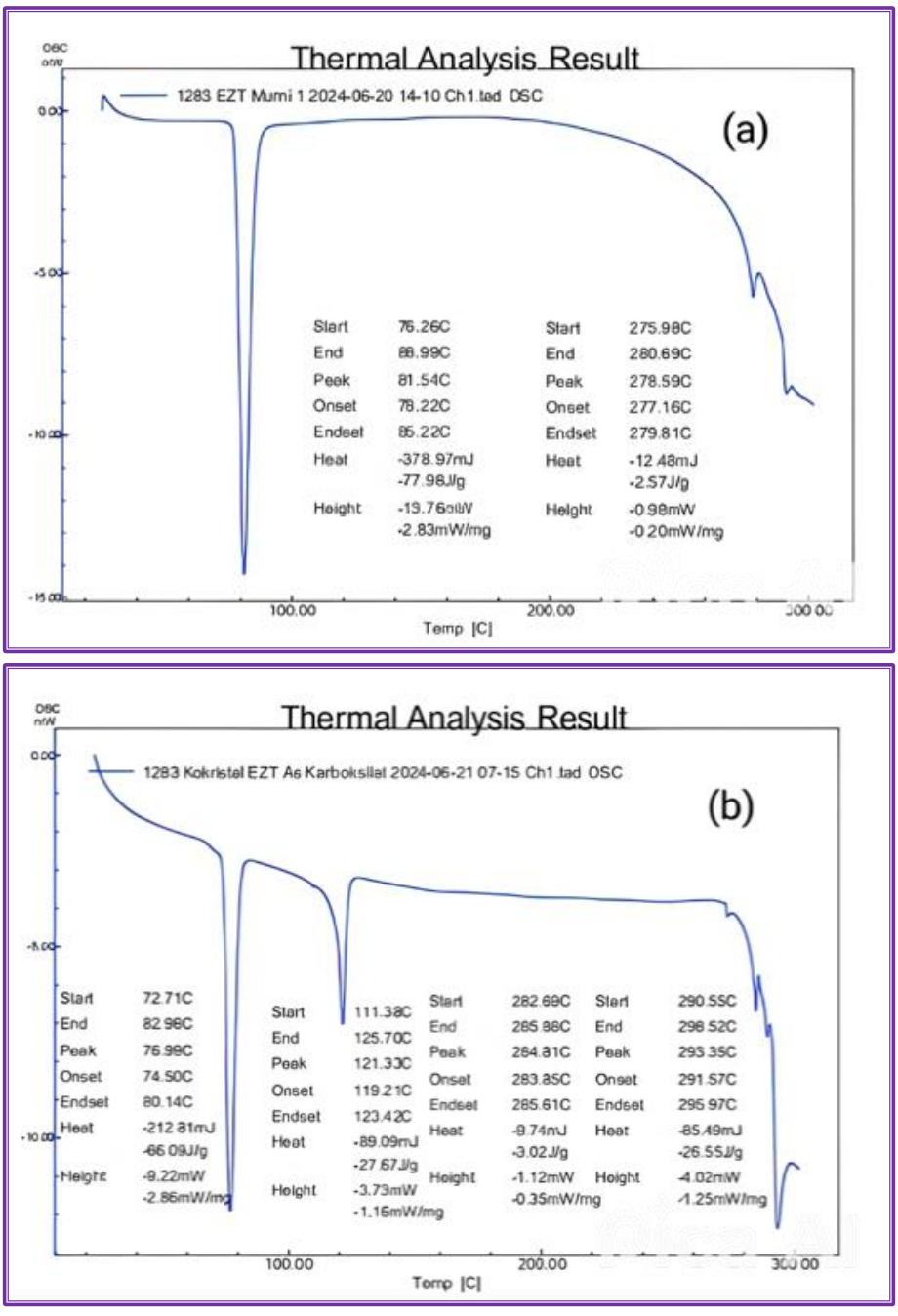

Figure 3: *DSC Thermograms: (a) Pure Ezetimibe (EZT); (b) Ezetimibe (EZT) Cocrystal*

As shown in Figure 3, the pure EZT sample presents a sharp endothermic peak at 81.54 °C, corresponding to its melting point. The cocrystal shows a lower melting point at 76.99 °C, indicating molecular interaction between EZT and the carboxylic acid coformer, which affects thermal stability.

Fourier Transform Infrared Spectroscopy (FTIR)

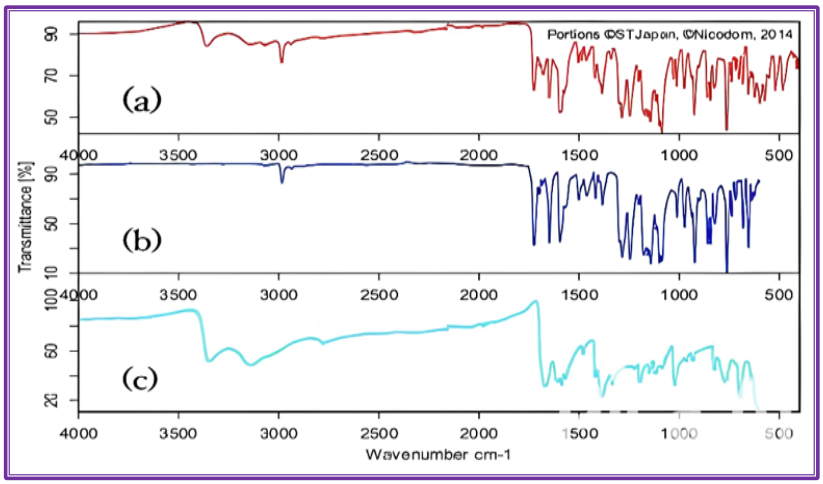

Figure 4: *FTIR Spectra: (a) Ezetimibe (EZT) Cocrystal; (b) Pure Ezetimibe (EZT); (c) Carboxylic Acid Coformer*

In Figure 4, the Fourier Transform Infrared (FTIR) spectrum of pure EZT shows a characteristic O–H stretching peak at 3071 cm^{-1}. The carboxylic acid coformer exhibits a peak at 3350 cm^{-1}. The EZT cocrystal on the other hand displays a new absorption peak at 3359 cm^{-1}, indicating hydrogen bonding between EZT and the conformer. These changes in crystallinity were consistent with PXRD patterns observed in similar cocrystals as reported by Ding *et al*. (2025); Nechipadappu and Balasubramanian (2023).

Scanning Electron Microscopy (SEM)

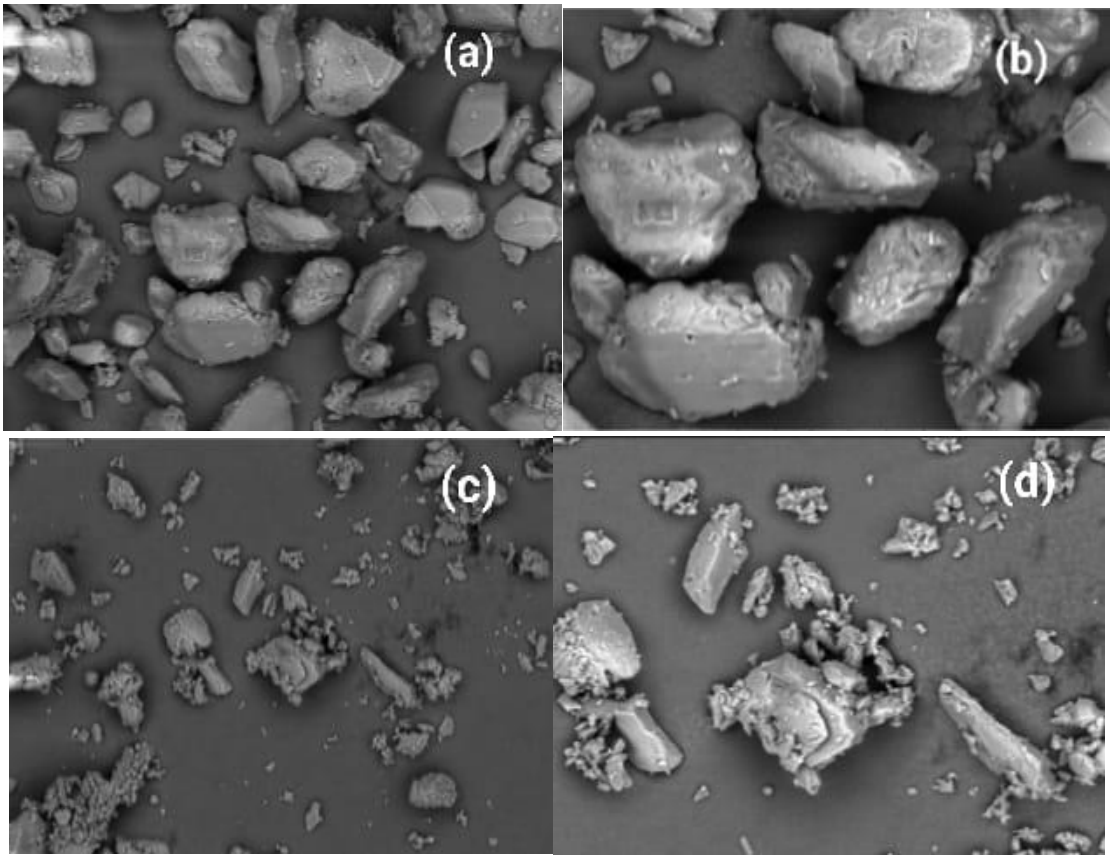

Figure 5: *SEM Micrographs: (a) Pure Ezetimibe (EZT) at 250×; (b) Pure Ezetimibe (EZT) at 500×; (c) Ezetimibe (EZT) Cocrystal at 250×; (d) Ezetimibe (EZT) Cocrystal at 500×*

Figure 5 shows that pure EZT particles appear larger and more defined. The cocrystal, however, presents smaller, irregularly shaped particles with rougher surfaces, indicating morphological changes due to co-crystallisation.

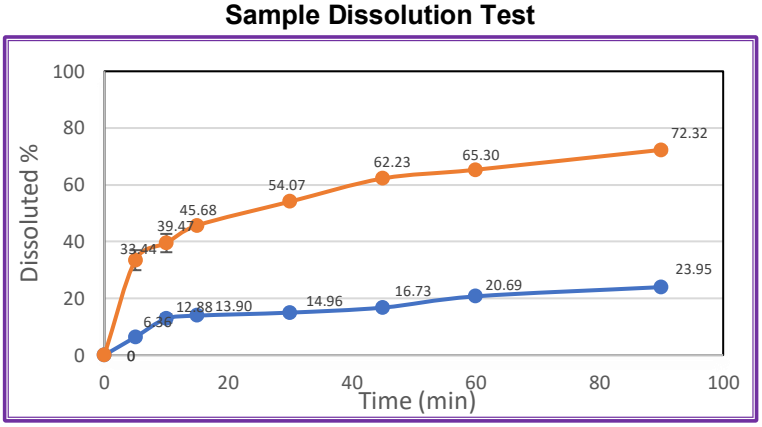

Figure 6: *Dissolution Profiles of (▬ : Ezetimibe (EZT) Pure) (▬ :Cocrystal Ezetimibe (EZT))*

Figure 6 illustrates the enhanced dissolution of the EZT cocrystal compared to pure EZT. At 15 minutes, the cocrystal achieved 49.13% dissolution, while pure EZT reached only 13.90%. At 60 minutes, the cocrystal reached 72.89%, compared to 20.69% for pure EZT. The improved dissolution is attributed to reduced crystallinity, altered particle morphology, and smaller particle size, all of which enhance solubility in the dissolution medium.

Discussion

The physicochemical characterisation of pure Ezetimibe (EZT) and its cocrystal form with carboxylic acid coformers was conducted using a series of analytical techniques, including Particle Size Analysis (PSA), Powder X-ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscopy (SEM), and dissolution studies complemented by UV-Vis spectrophotometry. These methods were selected to elucidate the structural modifications and performance enhancements attributed to the cocrystallisation process, particularly in relation to solubility and dissolution rate.

Based on the PSA results, cocrystallisation resulted in a significant reduction in particle size from 1.049 µm for pure EZT to 0.782 µm in the cocrystal form. This reduction implies an increased surface area, which in turn facilitates enhanced dissolution. This finding aligns with the study by Xiong *et al*. (2024), who demonstrated that the cocrystallisation of progesterone with selected carboxylic acids effectively decreased particle size and improved aqueous solubility. Similarly, Yang *et al*. (2022) also reported that particle engineering through cocrystallisation plays a pivotal role in enhancing the bioavailability of poorly soluble drugs such as Praziquantel.

Further structural evidence was provided by PXRD analysis. Pure EZT exhibited sharp diffraction peaks at 2θ = 22° and 35°, with intensities of 1,650 and 750, respectively. In contrast, the cocrystal displayed distinct modifications in peak positions and intensities, notably at 3,300 and 100, indicating a transformation in crystalline structure. This shift is indicative of the formation of a new solid-state form due to molecular interactions between EZT and the coformer. Comparable crystallographic changes have been observed in Praziquantel cocrystals with phenolic acids (Yang *et al*., 2022), as well as in imatinib-based systems (Ding *et al*., 2025). Moreover, a comprehensive review by D'Abbrunzo, Procida & Perissutti (2023) reinforces the significance of these solid-state transformations in the optimisation of pharmaceutical performance.

DSC analysis further supported the occurrence of structural modification. The melting point of pure EZT was recorded at 81.54 °C, while the cocrystal exhibited a slightly lower melting point at 76.99 °C. The reduction in melting point, along with the absence of an exothermic recrystallisation peak, suggests the

formation of a thermodynamically stable new phase. These thermal behaviours are consistent with those observed in cocrystals and salts of tranexamic acid, as reported by Nechipadappu and Balasubramanian (2023), in which changes in melting behaviour are linked to solid-state transformation and improved physicochemical stability.

FTIR spectroscopy provided additional evidence of molecular interaction between EZT and the coformer. The O–H stretching vibration appeared at 3,071 cm^{-1} in pure EZT and at 3,350 cm^{-1} in the coformer. In the resulting cocrystal, a new absorption band emerged at 3,359 cm^{-1}, indicating the formation of hydrogen bonds. This observation is in agreement with Karthammaiah, Venkataramanan & Solomon (2025), who demonstrated similar spectral shifts in a gallic acid–picolinic acid cocrystal salt hydrate system, where hydrogen bonding played a critical role in the stabilisation of the cocrystal lattice.

Morphological differences between pure EZT and the cocrystal were evident in SEM imaging. While pure EZT appeared as larger, smooth-surfaced particles, the cocrystal consisted of smaller, fragmented particles with a rougher texture. These morphological changes suggest successful crystal modification, which contributes to improved dissolution. Ding *et al*. (2025) emphasised that such morphological transformations enhance wettability and increase interaction with dissolution media, factors that are essential for the improved performance of BCS Class II drugs.

Dissolution testing confirmed the physicochemical enhancements conferred by cocrystallisation. Within 15 minutes, the cocrystal achieved a dissolution rate of 49.13%, in stark contrast to 13.90% observed for pure EZT. At 60 minutes, the dissolution of the cocrystal reached 72.89%, while the pure drug plateaued at 20.69%. These results highlight the synergistic impact of reduced crystallinity, smaller particle size, and modified surface properties on drug release. The improvement parallels findings by Xiong *et al*. (2024), who documented significant dissolution enhancement in cocrystals of progesterone, thereby confirming the viability of this strategy for drugs with limited aqueous solubility.

Table 1. Determination of Standard Curve

Concentration	Absorbance
4 ppm	0,340
6 ppm	0,412
8 ppm	0,461
10 ppm	0,656
12 ppm	0,740

To validate the accuracy of the dissolution quantification, UV-Vis spectrophotometry was employed, identifying the maximum absorbance wavelength of EZT at 287 nm. A standard curve generated from multiple concentrations yielded a linear regression equation of $Y = 0.0522x + 0.1042$ with a correlation coefficient (r) of 0.9759, indicating strong linearity and analytical reliability.

In summary, the comprehensive physicochemical characterisation confirmed that cocrystallisation of EZT with carboxylic acid coformers results in favourable modifications to particle size, crystalline structure, thermal behaviour, molecular interactions, morphology, and dissolution rate. These improvements collectively enhance the oral bioavailability of EZT and affirm the potential of cocrystal technology in overcoming formulation challenges associated with poorly water-soluble drugs.

Limitation and Future Scope

Despite the promising findings, this study has several important limitations that should be acknowledged. The entire evaluation was carried out under in vitro conditions, which means that the pharmacokinetic behaviour of the Ezetimibe (EZT) cocrystal—specifically its absorption, distribution, metabolism, and excretion (ADME)—has not been confirmed in vivo. As a result, the actual enhancement in bioavailability remains hypothetical and needs to be validated through further biological studies.

Another limitation lies in the lack of stability testing. The physical and chemical stability of the EZT cocrystal under various environmental factors such as temperature, humidity, and long-term storage was not assessed in this study. These aspects are crucial for determining the feasibility of large-scale manufacturing, packaging, and shelf-life for commercial pharmaceutical applications.

In addition, the research employed only a single type of coformer, namely a carboxylic acid derivative. Although this coformer was selected based on its GRAS status and hydrogen bonding capability, the use of only one coformer limits the generalisability of the findings. It remains uncertain whether other coformers might yield better physicochemical or pharmacokinetic performance. Furthermore, this study did not utilise computational approaches such as molecular docking or modelling. These methods could serve as valuable tools in the rational selection of coformers by predicting favourable drug–coformer interactions prior to experimental formulation.

Considering these limitations, future studies are recommended to include in vivo pharmacokinetic and pharmacodynamic evaluations to confirm the enhanced absorption and therapeutic efficacy of the EZT cocrystal. Stability studies—both accelerated and long-term—should also be conducted to ensure the robustness of the formulation during storage and transport. Moreover, screening a wider array of GRAS-listed coformers may uncover options with even better solubility and compatibility profiles. The integration of computational modelling and docking studies is also encouraged to facilitate a more efficient and targeted approach in cocrystal design.

Conclusion

The formation of ezetimibe (EZT) cocrystals with carboxylic acid coformers successfully improved the physicochemical properties and solubility of EZT. Characterisation tests showed smaller particle size changes, the formation of new crystalline phases, and a decrease in melting point in EZT cocrystals compared to pure EZT. Additionally, EZT cocrystals exhibited a significant increase in solubility in dissolution tests, with a higher dissolution percentage compared to pure EZT. Thus, cocrystallisation has proven to be an effective method for enhancing the absorption and therapeutic potential of ezetimibe as an antihyperlipidemic drug.

Conflict of Interest

The authors declare that they have no competing interests.

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