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Research Article

A Potential Catechin Co-Crystal Strategy with Succinic Acid as Coformer to Improve Solubility

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ABSTRACT

Catechin, a flavonoid with potential health benefits, is indeed only slightly soluble in water, which can limit its bioavailability and effectiveness. One approach to enhance its solubility is co-crystallization or cocrystal, where catechin is combined with succinic acid as coformer to modify its crystalline structure. In this study, catechin-succinic acid cocrystals were prepared at a 1:1 mol ratio using Liquid Assisted Grinding Method (LAG) with ethanol p.a. as solvent. Physicochemical characterization was performed to confirm cocrystal formation. Crystallinity and structural properties were analyzed using FTIR (Fourier transform infrared spectrometry), XRD (X-ray diffraction spectrometry), and SEM (Scanning Electron Microscopy), while thermal behavior and melting point were evaluated using DSC (Differential Scanning Calorimetry). The aqueous solubility of cocrystal was determined to assess the effect of cocrystallization on the solubility enhancement of catechin. Thermal analysis observed change in melting points of cocrystals compared pure catechin and succinic acid that indicated eutectic compound were formed during the co-crystallization process. The result of FTIR analysis of cocrystals was shifted in the wavenumber spectrum compared to pure catechin and succinic acid indicated hydrogen bond between catechin and succinic acid was formed. SEM and XRD of crystal indicated a difference morphology and diffractogram compared to catechin and succinic acid that indicated new crystal was formed. The solubility test result obtained 124.58 mg/100 mL (catechin) and 151 mg/100 mL (cocrystal). Cocrystal of catechin and succinic acid have been successfully formed by LAG method and increased solubility.

Keywords: Cocrystal, Catechin, Succinic acid, Coformer, Solubility

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Introduction

Catechin is a naturally occurring polyphenolic compound classified within the flavonoid group, which is widely distributed in various plant species and contributes significantly to their pharmacological and nutritional properties. It is predominantly found in *Uncaria gambir* (gambir) and *Camellia sinensis* (tea), but is also present in other natural sources such as coffee, rose leaves, snow peas, red and black grapes, strawberries, and apricots [1, 2]. Based on various reports, pure catechin exhibits very strong antioxidant activity, with IC_{50} values ranging from 0.13 to 3.12 μg/mL, depending on the assay method and solvent used [3–6]. These values indicate that catechin can act effectively against oxidative stress-related diseases including cardiovascular disorders (such as hypertension, endothelial dysfunction, and atherosclerosis), neurodegenerative diseases (such as Alzheimer's, Parkinson's, and Huntington's diseases), and cancers [7]. Several studies have also demonstrated catechin's ability to inhibit tumor growth and function as a chemopreventive agent through its radical scavenging and cell cycle–modulating mechanisms [8–12].

Despite its broad pharmacological potential, the therapeutic efficacy of catechin is severely limited by its poor aqueous solubility, reported to be approximately 1:1100–1:1200 in water, resulting in reduced dissolution, absorption, and oral bioavailability [13]. *In vivo* studies have shown that the plasma concentration of catechin rarely reaches the effective levels observed in vitro, highlighting a significant gap between its pharmacodynamic potential and pharmacokinetic performance. Increasing the dosage to compensate for low absorption is not a viable strategy, as catechin exhibits dose-dependent toxicity, where adverse effects correlate with higher systemic exposure. Therefore, strategies to enhance the solubility and bioavailability of catechin are essential for achieving optimal therapeutic outcomes [14, 15].

One effective strategy to enhance the therapeutic performance of poor water-soluble compounds is through cocrystallization or cocrystal method. Co-crystallization has gained significant attention in pharmaceutical development as promising approach to improve the solubility, dissolution rate, and bioavailability. Cocrystals are defined as crystalline solids materials composed of two or more different molecular entities, typically an active pharmaceutical ingredient (API) and a co-former (Cocrystal former/coformer), which may be a small molecule or a polymer. These systems can be the method of choice in pharmaceutical science due to their ability to modify the physicochemical properties of the API. The formation of cocrystals involves non-covalent interactions between API and coformer such as hydrogen bonding, van der Waals forces, and π-π stacking, which contribute to their unique structural characteristics and properties [16]. The development of cocrystals offers a promising strategy for improving the performance of poorly soluble drugs, as they can enhance dissolution rates and therapeutic efficacy. Moreover, cocrystallization can mitigate issues related to polymorphism and improve the stability of solid forms, which are critical factors in drug formulation and development.

The choice of a suitable coformer is a key determinant in successful cocrystal formation, as it influences not only solubility but also solid-state stability and bioavailability. Succinic acid, a dicarboxylic acid generally recognized as safe (GRAS), has been widely utilized as a coformer due to

its ability to form robust hydrogen bonds and its favorable physicochemical characteristics [17]. Previous studies have shown that cocrystallization of various poorly soluble drugs with succinic acid, such as piperine and itraconazole, markedly enhanced their solubility and dissolution rates [18, 19]. Hence, the formation of a catechin–succinic acid cocrystal could potentially enhance the aqueous solubility and physicochemical stability of catechin while improving its bioavailability and pharmacological performance.

The objective of this study is to investigate the cocrystallization of catechin with succinic acid as a coformer, focusing on the synthesis, physicochemical characterization, and solubility enhancement of the resulting cocrystal, as well as its potential pharmaceutical implications.

Materials and Methods

Materials

Catechin (*sigma Pcode*: 102687710 ≥ 98%), succinic acid (*sigma Pcode*: 1003593083, ACS *Reagent* ≥ 99%), ethanol (CAS-NO-64-1745), potassium dihydrogen phosphate (CAS-NO-7778-77-0), sodium hydroxide (CAS-NO-1310-73-2), DPPH (1,1-diphenyl-2-picrylhydrazyl) were all purchased from Sigma-Aldrich; and aquadest (Medica Laborta).

Cocrystal preparation

The cocrystal was prepared by liquid-assisted grinding using ethanol as solvent. Catechin (0.072 g) and succinic acid (0.029 g) were accurately weighed in a molar ratio of 1:1 and thoroughly mixed using a mortar and pestle to ensure homogeneous blending of the components. Subsequently, 2 mL of ethanol was gradually added to the mixture while grinding until a viscous paste was obtained. The resulting mass was allowed to stand at ambient temperature (25 °C) for approximately 7–8 days to facilitate slow evaporation of the solvent and complete drying of the cocrystals. The obtained solid was then collected and stored in a desiccator until further characterization.

Cocrystal characterization

Cocrystal characterization was carried out using Differential scanning calorimetry (DSC), Fourier transform infrared spectrometry (FTIR), Powder X-ray Diffraction spectrometry (PXRD), and Scanning Electron Microscopy (SEM).

DSC

Thermal analysis was performed using a Differential Scanning Calorimeter on pure catechin, succinic acid, and the catechin–succinic acid cocrystal. Approximately 3.800 mg of catechin, 14.400 mg of succinic acid, and 5.300 mg of the cocrystal sample were accurately weighed and placed into aluminum pans, which were hermetically sealed. The samples were heated from 30 °C to 300 °C at a constant heating rate of 20 °C/min under a nitrogen atmosphere. The obtained thermograms were analyzed to identify thermal events and to confirm the formation of the new crystalline phase.

FTIR

FTIR spectra were recorded for pure catechin, succinic acid, and the catechin–succinic acid cocrystal to investigate possible intermolecular interactions. Approximately 1 mg of each sample was placed directly onto the diamond crystal of an Attenuated Total Reflectance (ATR) accessory and gently pressed to ensure proper contact. The spectra were collected over the range of 4000–400 cm^{-1} with an appropriate resolution. Characteristic band shifts were analyzed to confirm hydrogen bonding and other functional group interactions between the API and coformer.

XRD

The crystalline nature of pure catechin, succinic acid, and the catechin–succinic acid cocrystal was evaluated using Powder X-Ray Diffraction. Approximately 1 mg of each sample was placed onto the sample holder and flattened to form a smooth surface. The measurements were carried out using Cu Kα radiation (λ = 1.5406 Å) at an operating voltage of 40 kV and a current of 30 mA. Data were collected over a 2θ range of 5°–50° using continuous scanning mode. The resulting diffraction patterns were compared to identify the formation of new peaks indicative of cocrystal formation.

SEM

Morphological analysis of pure catechin, succinic acid, and the catechin–succinic acid cocrystal was conducted using a Scanning Electron Microscope. Approximately 10 mg of each sample was fixed onto an aluminum stub using double-sided carbon adhesive tape. The powders were evenly distributed to ensure clear imaging. The samples were observed under an accelerating voltage of 14 kV at appropriate magnifications. Micrographs were obtained to compare surface morphology and crystal habit between the pure components and the cocrystal.

Solubility test

The solubility study was conducted to compare the aqueous solubility of pure catechin and the catechin–succinic acid cocrystal. An excess amount of each sample, equivalent to 60 mg of catechin, was added to 10 mL of distilled water. The solutions were stirred using a magnetic stirrer at room temperature for 1 hour, each experiment performed in triplicate. Following stirring, the mixtures were sonicated for 15 minutes to ensure complete dissolve solution, and then filtered through Whatman No. 42 filter paper to remove undissolved residues. The filtrates were subsequently analyzed using a UV–Visible spectrophotometer to determine the concentration of dissolved catechin (n=3).

Results and Discussion

The appearance of the obtained cocrystal compared to pure catechin and succinic acid is shown in Figure 1. The characterization of catechin cocrystals with succinic acid as a coformer has provided valuable insights into their potential benefits in pharmaceutical applications. The formation of cocrystals

is evidenced by various characterization techniques, indicating significant alterations in the properties of the original compounds.

Figure 1 Catechin (left); succinic acid (middle); and cocrystal (right).

DSC Analysis

DSC analysis was performed to evaluate the thermal behavior and confirm the formation of the catechin–succinic acid cocrystal. DSC provides insights into thermodynamic transitions such as melting, recrystallization, and solid-state transformation that occur when the sample is exposed to heat. The DSC thermograms of pure catechin, succinic acid, and the cocrystal are shown in Figure 2. Pure catechin exhibited two distinct endothermic peaks at 138.58 °C and 176.59 °C, corresponding to its crystalline melting transitions, while succinic acid showed a single sharp melting point at 198.03 °C. In contrast, the catechin–succinic acid cocrystal displayed a single, broader endothermic peak at 94.44 °C, indicating a reduction in melting temperature relative to both parent compounds. This downward shift in melting point signifies the formation of a new crystalline phase with lower lattice energy, resulting from intermolecular hydrogen bonding between catechin and succinic acid. The reduced melting point of the cocrystal also suggests enhanced solubility and improved thermodynamic stability compared to pure catechin. These findings align with previous studies showing that the appearance of new endothermic events and melting point shifts in DSC thermograms are characteristic indicators of successful cocrystal formation [17, 20, 21].

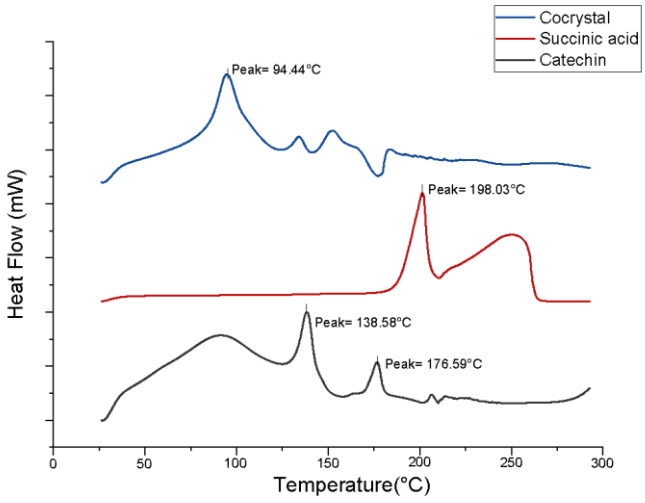

Figure 2 Curve of DSC for cocrystal, succinic acid, and cathecin.

FTIR Analysis

Fourier-transform infrared (FTIR) spectroscopy was employed to investigate the molecular interactions and functional groups involved in the formation of the catechin–succinic acid cocrystal [22].

Figure 3 presents the FTIR spectra of pure catechin, succinic acid, and the catechin–succinic acid cocrystal, illustrating the differences in characteristic absorption bands among the three samples. The FTIR spectra of pure catechin showed characteristic absorption bands in the 3000–3500 cm^{-1} region, corresponding to O–H stretching vibrations, while succinic acid exhibited distinct peaks at approximately 1700 cm^{-1} (C=O stretching) and 1400 cm^{-1} (C–H bending). In the cocrystal spectrum, noticeable shifts and broadening of these bands were observed, indicating the formation of new intermolecular interactions. Specifically, the broadening and downshift of the O–H stretching band in the cocrystal suggest the establishment of hydrogen bonds between catechin and succinic acid, confirming the presence of strong non-covalent interactions. Likewise, the shift of the C=O stretching vibration of succinic acid to a lower wavenumber supports its participation in hydrogen bonding with catechin hydroxyl groups. Such spectral changes are consistent with successful cocrystal formation, where hydrogen bonding plays a crucial role in stabilizing the crystalline lattice and enhancing solubility [23–25].

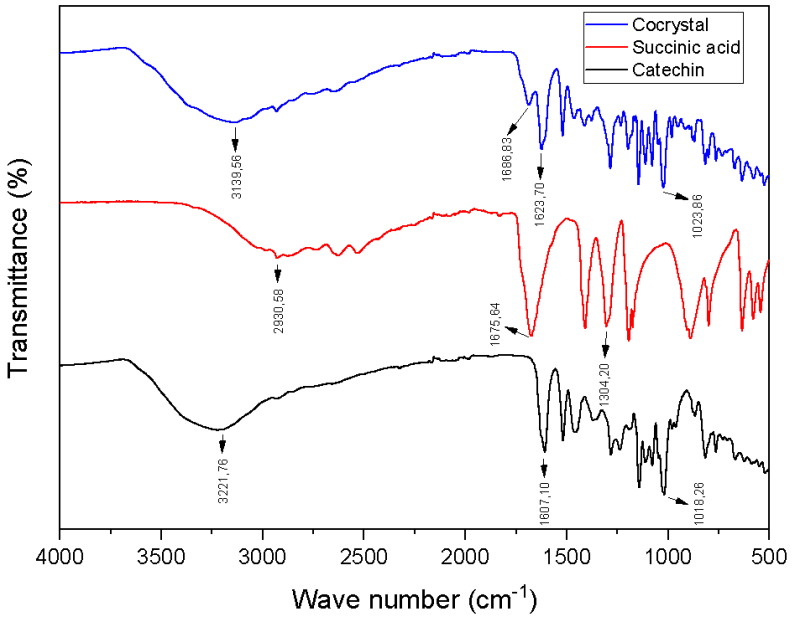

Figure 3 Spectra FTIR for for cocrystal, succinic acid, and cathecin.

The illustrated structure (Figure 4) demonstrates the formation of intermolecular hydrogen bonds between catechin and succinic acid, primarily involving hydroxyl groups of catechin and carboxyl groups of succinic acid. These interactions lead to the formation of a heterosynthon, which stabilizes a new crystalline phase and supports the cocrystal formation. The establishment of this hydrogen-bonding network is consistent with the FTIR shifts observed and contributes to the modification of the crystal lattice, ultimately enhancing solubility.

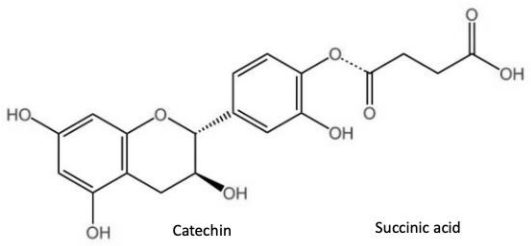

Figure 4 Structural illustration of cocrystal catechin-succinic acid.

XRD Analysis

X-ray diffraction (XRD) analysis is a powerful technique used to examine the crystalline characteristics of materials and to confirm the formation of cocrystals. The XRD patterns of the catechin–succinic acid cocrystal showed distinct differences compared to those of the individual components, indicating the successful formation of a new crystalline phase (Figure 5).

The XRD pattern of pure catechin exhibited characteristic peaks at 2θ value of 16.5°, 19.05°, and 23.73°. Meanwhile, succinic acid showed distinct diffraction peaks at 2θ value of 16.09°, 20.03°, 26.16°, 31.47°, and 38.04°. In contrast, the XRD pattern of the catechin-succinic acid cocrystal differed significantly from those of the individual components. It's showed several new diffraction peaks that were absent in either of the parent compounds, signifying the generation of a unique crystal lattice. The cocrystal exhibited new crystalline peaks at 2θ value of 13.78°, 16.93°, 18.95°, 19.69°, 23.44°, 25.81° and 31.16°. These findings confirm that the cocrystallization process effectively modified the solid-state structure of catechin and resulted in the development of a new crystalline entity with distinct structural characteristics [26].

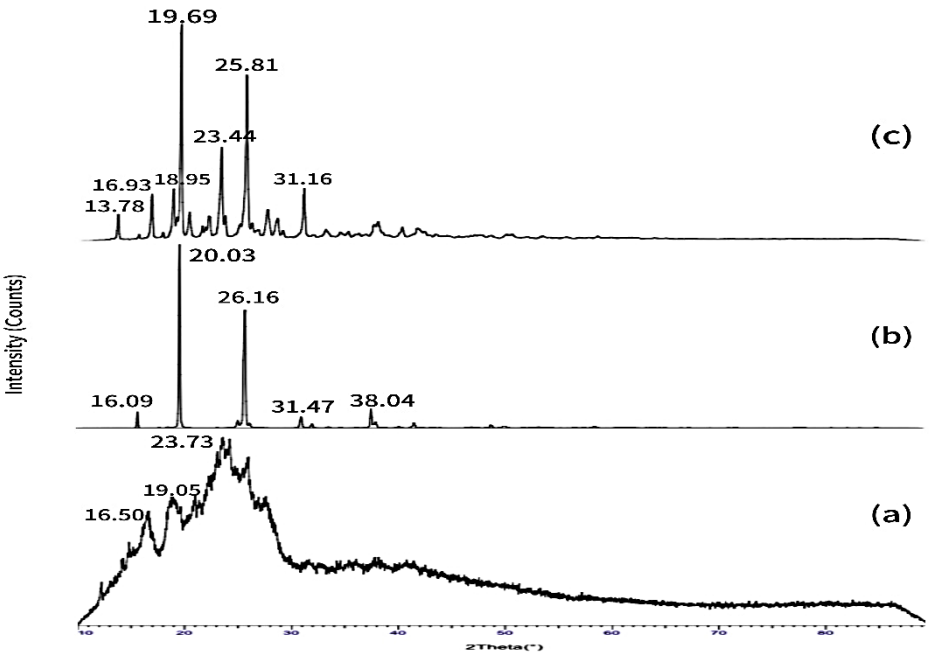

Figure 5 The XRD pattern for (a) catechin; (b) succinic acid; and (c) cocrystal.

SEM Analysis

Scanning Electron Microscopy (SEM) was employed to examine the surface morphology and particle characteristics of the samples. The SEM images of the catechin–succinic acid cocrystal exhibited distinct morphological features compared to those of the individual components, demonstrating the influence of cocrystallization on the physical properties of catechin [27].

Pure catechin showed irregularly shaped particles with relatively smooth surfaces, while succinic acid presented well-defined, crystalline particles with sharp edges. In contrast, the catechin–succinic acid cocrystal displayed agglomerated particles with rough and uneven surface textures (Figure 6). The observed changes in morphology confirm the occurrence of cocrystallization, suggesting strong intermolecular interactions between catechin and succinic acid that led to the formation of a new crystalline structure.

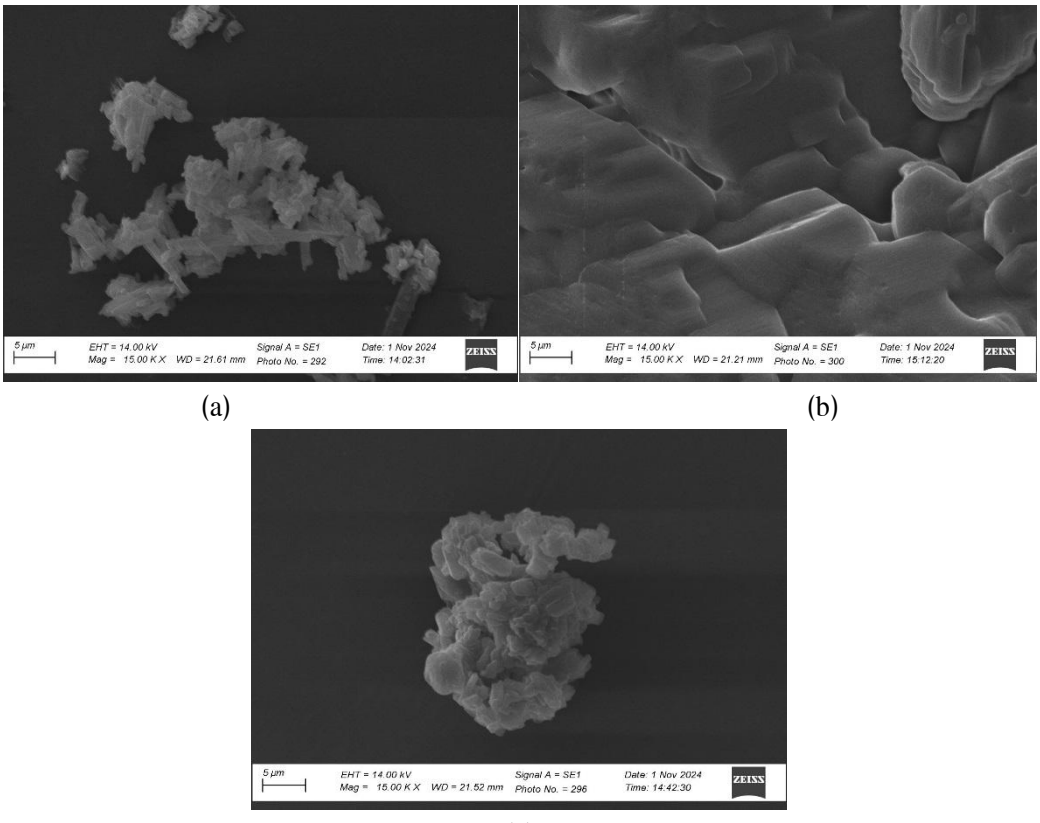

Figure 6 Photomicrograph of catechin (a), succinic acid (b), and cocrystal (c) 15.000x magnification.

Solubility studies

The solubility of a compound is a critical determinant of its bioavailability and therapeutic performance, particularly for poorly soluble drugs such as catechin. Solubility measurements were conducted in distilled water and the concentration was determined by UV-Vis spectrophotometry (n=3). The solubility studies revealed that the catechin– succinic acid cocrystal exhibited a marked improvement in aqueous solubility compared to pure catechin, increasing from 124.58 mg/100 mL to 151 mg/100 mL, corresponding to an enhancement of approximately 21.2%.

This enhancement indicates that cocrystallization effectively modified the physicochemical properties of catechin, leading to better dissolution characteristics and may contribute to improved bioavailability, although further *in vivo* studies are required. The observed increase in solubility can be attributed to the formation of a new crystalline phase that alters the crystal lattice energy and molecular packing of catechin. The incorporation of succinic acid as a coformer disrupts the strong intermolecular hydrogen bonding network of pure catechin, thereby reducing lattice energy and increasing surface wettability [18].

Several mechanisms may contribute to this improvement. The formation of strong intermolecular hydrogen bonds between catechin and succinic acid not only stabilizes the cocrystal structure but also enhances molecular interaction with water molecules, facilitating faster dissolution. Similar findings were reported in studies on flavonoid-based and succinic acid–based cocrystals, where hydrogen-bond-driven lattice modifications significantly improved solubility and dissolution rates [28, 29]. Furthermore, the increased solubility observed in the catechin–succinic acid system aligns with the general trend observed for cocrystals involving dicarboxylic acid coformers, which can introduce channel-like packing motifs that facilitate solvent penetration [30]. These findings collectively confirm that cocrystallization represents a promising strategy for enhancing the solubility and pharmaceutical performance of poorly water-soluble natural compounds such as catechin.

Conclusions

The catechin–succinic acid cocrystal was successfully synthesized using the liquid-assisted grinding (LAG) method. Characterization by DSC, FTIR, XRD, and SEM confirmed the formation of a new crystalline phase with distinct physicochemical properties. The cocrystal exhibited significantly enhanced solubility compared to pure catechin, attributed to strong intermolecular hydrogen bonding and reduced lattice energy. These findings demonstrate that cocrystallization with succinic acid is an effective strategy to improve the solubility and potential bioavailability of catechin for pharmaceutical applications.

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