ORIGINAL ARTICLE

Crystal Engineering of Ibuprofen and Caffeine by Cocrystal Formation Using Solvent Evaporation and Slurry Methods

Mikhania Christiningtyas Eryani*, Yudi Wicaksono, Budipratiwi Wisudyaningsih, Kuni Z. Barikah, Hery Diar Febrianto

Active Pharmaceutical Ingredients and Excipients (APIE) Research Group, Faculty of Pharmacy, University of Jember, Jember, Indonesia

ABSTRACT

Ibuprofen is a pharmaceutical active compound used to treat mild to moderate pain and fever. However, ibuprofen has low solubility in water. One method to increase solubility is cocrystal formation. The ibuprofen cocrystal was prepared in this study using caffeine as a coformer at a 1:1 molar ratio via solvent evaporation and slurry methods. The results of the XRD and thermal analysis of the sample indicate that a new solid phase is formed in the specific sa mple, which is different from both of its constituent components. Morphologically, the resulting cocrystals show a change in shape from their constituent compounds as well as a change in size. The solubility test results show that cocrystal formation is able to increase the solubility of ibuprofen. The conclusion of this study is that ibuprofen cocrystals can be formed with the coformer caffeine at a molar ratio of 1:1 using the slurry method and solvent evaporation.

Keywords: ibuprofen, caffeine, cocrystal

Correspondence:
Mikhania Christiningtyas Eryani
Active Pharmaceutical Ingredients and Excipients (APIE) Research Group, Faculty of Pharmacy, University of Jember, Jember, Indonesia

Email:
mikhaniachristi@unej.ac.id

Article History:
Received: 4 Nov 2025
Revised: 27 Apr 2026
Accepted: 26 Jun 2026

DOI:
https://doi.org/10.25077/jsfk.13.1.15-20.2026

Citation:
Eryani MC, Wicaksono Y, Wisudyaningsih B, Barikah KZ, Febrianto HD. Crystal Engineering of Ibuprofen and Caffeine by Cocrystal Formation Using Solvent Evaporation and Slurry Methods. J Sains Farm Klin. 2026;13(1):15-20

Access This Article

Introduction

Ibuprofen is a nonsteroidal anti-inflammatory drug used to treat mild to moderate pain and fever. Based on its solubility and permeability, ibuprofen belongs to Biopharmaceutical Classification System (BCS) class II, which are compounds with low solubility but good permeability. Ibuprofen is practically insoluble in water, with a solubility of 46.9 μg/ml at 37°C and 29.1 μg/ml at 25°C [1]. In BCS class II drugs, drug dissolution in gastrointestinal fluids is the rate-limiting step in drug absorption [2].

Methods that can be used to increase the dissolution/solubility of ibuprofen include solid dispersion formation, inclusion complexation, and salt formation [3,4,5]. Additionally, crystal engineering or crystal engineering through cocrystal formation can also be used as one technique to improve the dissolution of active ingredients. The cocrystal technique is a simple technique performed by combining two or more solid molecules to form a single crystal lattice through noncovalent interactions that interact via hydrogen bonds (most common), halogen bonds, and π-π interactions [6]. Cocrystals offer enhanced solubility without altering the ionic structure of the drug, thereby providing better stability. Cocrystals are utilized to enhance the physicochemical properties of pharmaceutical active ingredients without altering their molecular structure or pharmacological activity. The physicochemical properties that have been successfully improved include solubility, stability, bioavailability, and mechanical properties [1]. Cocrystals are composed of an active pharmaceutical ingredient and a coformer. The high solubility of the coformer is directly related to the increased solubility and dissolution of the active pharmaceutical ingredient cocrystal [7]. Caffeine is one of the compounds that can be used as a coformer. Caffeine is commonly employed as a coformer in multicomponent crystal systems due to its ability to form strong and directional

hydrogen bonds through its carbonyl and nitrogen groups. Multicomponent investigations of caffeine crystals have been extensively explored, including the development of caffeine cocrystals with hydroxy-2-naphthoic acid. These systems exhibit characteristic carboxylic acid dimer hydrogen bonding, supported by the formation of hydroxyl–caffeine heterosynthons, which play a key role in stabilizing the crystal structure [8]. Caffeine is an alkaloid derivative compound found in coffee (*Coffea* sp.). Caffeine is soluble in water (1:50), alcohol (1:66), or chloroform (1:6), but less soluble in ether. The solubility of caffeine increases in hot water (1:6 at 80 °C) or hot alcohol (1:25 at 60 °C). The higher solubility of caffeine in water compared to ibuprofen allows caffeine to be used as a coformer in ibuprofen cocrystals.

The most common method used in cocrystal formation is solvent evaporation. In this method, both the drug and the coformer are in the molecular phase, allowing for molecular interactions between the components [6]. However, the use of large quantities of organic solvents subsequently became a separate consideration in the development of cocrystals. Another formation method that can be used is the slurry method, which uses a smaller amount of solvent, thus reducing the risk of residual organic solvent remaining.

This study aims to form ibuprofen-caffeine cocrystals using the solvent evaporation and slurry methods. The cocrystals were prepared with an active ingredient to coformer ratio of 1:1. The formation of the cocrystals was analyzed using SEM, PXRD, and DSC.

Methods

Materials

Ibuprofen (SI Group, USA), caffeine (CSPC Innovation Pharmaceutical , China), ethanol (Merck), aquadest (Aneka Kimia), sodium hydroxide (Merck), potassium dihydrogen phosphate (Merck), potassium hydrogen phosphate (Merck)

Co-crystal Formation by Solvent Evaporation Method

The ibuprofen-caffeine cocrystal was prepared in a 1:1 molar ratio. The required amounts of ibuprofen and caffeine were weighed according to their molar ratio and dissolved separately in 10 mL ethanol solvent. The two solutions were then mixed and stirred using a magnetic stirrer (e.g., IKA® C-MAG HS 7) until homogeneous. The resulting mixture was then evaporated at room temperature for 72 hours. The crystals obtained are then stored in a desiccator [9].

Co-crystal Formation by Slurry Method

The slurry method was performed by making a physical mixture of ibuprofen and caffeine in a 1:1 molar ratio, totaling 1 gram. 20.0 ml of ethanol solvent was then added to the physical mixture until a suspension was formed. The suspension was then stirred using a magnetic stirrer and evaporated at room temperature. The crystals obtained are then stored in a desiccator [9].

Crystalinity

Crystallinity analysis was performed using X-ray diffraction (PXRD) (Empyrean, Netherland). The testing was conducted at angles of 2θ 5-60°. The formation of a new solid crystal phase or cocrystal can be indicated by the appearance of a diffractogram profile that differs from the pure diffractograms of the two constituent materials [9].

Thermal analysis

Thermal analysis was performed using a Differential Scanning Calorimeter (DSC). A 5 mg sample was weighed, placed in a sample pan, and then inserted into the DSC instrument. The instrument was set to a heating rate of 5°C. The melting point of the sample is observed thru the resulting thermogram profile. The formation of cocrystals is indicated by the formation of a new solid phase on the thermogram with a melting point different from that of its two constituent materials [9].

Surface morphology

The crystal morphology of each sample can be observed using a Scanning Electron Microscope (SEM). The powder samples were placed on an aluminum sample holder and coated with platinum to a thickness of 10 nm. The samples were then observed at various magnifications using the SEM instrument. The voltage was set to 15 kV and the current to 12 mA. Cocrystals form when a new crystal morphology is observed that is different from the crystal morphologies of its two constituent materials [10].

Solubilty test

The determination of solubility was performed on ibuprofen samples and ibuprofen-caffeine cocrystal samples. A quantity of sample equivalent to 20 mg of ibuprofen was weighed and placed into 50 mL of buffer phosphate medium in the solubility testing chamber. The testing was conducted at a temperature of 37±0.5 °C with constant stirring. Samples were taken at hours 1, 2, 3, 4, 5, and 6, each 5 ml, and then their concentration was determined using a UV-Vis spectrophotometer (Genesys 10S UV Vis) at a wavelength of 222 nm [11].

RESULT AND DISCUSSION

Cocrystals are one form of solid modification used to alter the physicochemical properties of drug substances, particularly their solubility [9]. Increasing drug solubility thru the cocrystallization method has been widely studied and proven successful. A cocrystal is a crystalline complex consisting of two or more neutral molecular constituents bound together in a crystal lattice thru noncovalent interactions (hydrogen bonding is often used). Ibuprofen is a pharmaceutical active compound that is effective as an analgesic and antipyretic. The structure of ibuprofen has one hydroxyl group and one carbonyl group, which have the potential to bond with the methyl group on caffeine, forming hydrogen bonds and thus creating a cocrystal.

The formation of ibuprofen-caffeine cocrystals was carried out at a 1:1 molar ratio and using two methods: solvent evaporation and slurry. In ibuprofen–caffeine cocrystals, a 1:1 ratio is selected because it corresponds to the most stable intermolecular interaction stoichiometry, particularly the formation of hydrogen bonds between the carboxylic group of ibuprofen and the acceptor sites of caffeine. This ratio facilitates the formation of an ordered heterosynthon within the crystal lattice, resulting in a stable cocrystal phase. The crystal characterization performed includes crystallinity, thermal analysis, and crystal morphology.

The results of the thermal analysis using DSC show the presence of a new endothermic peak that is different from the constituent compounds. The presence of the new endothermic peak indicates the formation of a new solid phase in the sample. The formation of a cocrystal is indicated by the formation of a new solid phase on the thermogram with a melting point different from that of its two constituent materials. Based on **Figure 1**, the melting point of ibuprofen is 75.7°C and caffeine is 237.5°C. This is consistent with the literature, which states that the melting point of ibuprofen ranges from 75-78°C, while caffeine is 235-239°C [12,13]. The melting point of the cocrystal obtained from the slurry method is 181°C, while the cocrystal formed from the solvent evaporation process has a melting point of 147.5°C. In the cocrystallization process, most cocrystals will have a melting point between the melting points of the coformer and the active ingredient [14,15]. The peak at point c at the end of the graph represents an endothermic event at a higher temperature, typically associated with the melting of a crystalline structure. This indicates enhanced thermal stability, suggesting the possible formation of a new phase, such as a cocrystal, with stronger intermolecular interactions than the original components.

The melting point of cocrystals produced by slurry and solvent evaporation methods can differ. This difference is caused by variations in crystal morphology, crystal size, and purity levels resulting from each method. The slurry method tends to produce larger and more uniformly sized crystals, while solvent evaporation can yield smaller and less regular cocrystals or may not form them perfectly. Consequently, the melting point of cocrystals made by the solvent evaporation method is lower compared to cocrystals made by the slurry method [16].

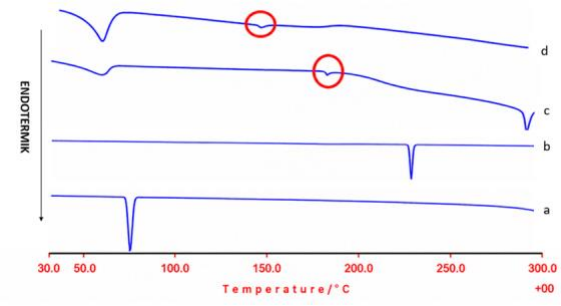

Figure 1. Thermogram of ibuprofen (a), caffeine (b), ibuprofen-caffeine cocrystal by slurry method (c), ibuprofen-caffeine cocrystal by solvent evaporation method (d)

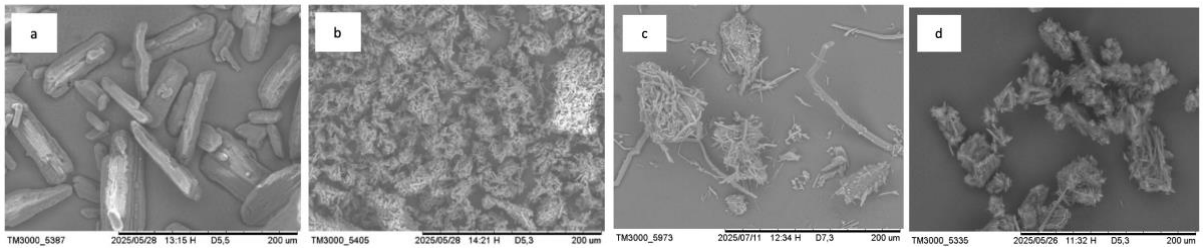

Figure 2. Crystal morphology of Ibuprofen (a), Caffeine (b), Ibuprofen-Caffeine Cocrystal by Slurry Method (c), Ibuprofen-Caffeine Cocrystal by Solvent Evaporation Method (d)

To determine the crystal morphology, an SEM test was conducted. The crystal morphology obtained from the SEM results, as shown in **Figure 2**, indicates that ibuprofen has a present as block-shaped particles [17]. Meanwhile, caffeine exhibits a powder-like morphology, as stated that caffeine has a description of being a white powder [18]. Morphologically, the resulting cocrystals show a change in shape from their constituent compounds. The results of this SEM analysis indicate that there is an interaction between the two substances, affecting the crystal morphology of each substance [19].

The purpose of powder X-ray diffractometer (PXRD) characterization is to determine the solid-state interaction between two solid components and whether a new crystalline phase will form. If the X-ray diffraction pattern shows a diffraction pattern different from its constituent components, such as comparing the position and intensity of the lines on the diffractogram, it can be concluded that a new solid phase or cocrystal has formed (20). The process of cocrystal formation causes changes in the XRD pattern, which will show some new peaks and peaks that identify the formation of the cocrystal. The PXRD results can be seen **in Figure 3**.

From **Figure 3**, in the cocrystals made by the slurry and solvent evaporation methods, new peaks and spikes appear on the diffractogram at angles of 2θ 6.01°; 14.01° and 31.01°. The appearance of new peaks on the diffractogram indicates the formation of new crystal planes as a result of the interaction between ibuprofen and caffeine. From Figure 3, differences in peak intensity were also observed between the cocrystals produced by slurry and solvent evaporation. The XRD results of cocrystals made by the slurry method and solvent evaporation can differ due to variations in crystal arrangement (orientation), particle size, and sample density, which affect the recorded diffraction pattern. In the slurry method, crystals are produced with particles that are not uniformly oriented, resulting in diffraction patterns that tend to show lower, broader, and less defined peak intensities. Meanwhile, cocrystal formation by solvent evaporation allows particles to precipitate and arrange themselves more regularly as the solvent evaporates, resulting in better crystal orientation and sharper peaks [16].

The results of the sample solubility test, as shown in Figure 4, indicate that cocrystal formation can improve the solubility of ibuprofen. The solubility of ibuprofen cocrystals prepared by the solvent evaporation method is higher than that of those produced by the slurry method, which is related to differences in the quality of crystal phase formation. Based on XRD and DSC results, crystals obtained from the slurry method tend to have non-uniform particle orientation, resulting in diffraction patterns with lower intensity, broader, and less sharp peaks, indicating the

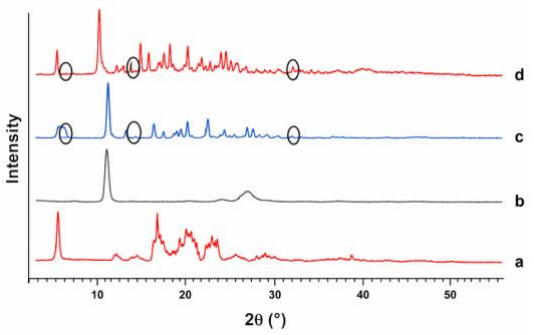

Figure 3. Diffractogram of Ibuprofen (a), Caffeine (b), ibuprofen-caffeine cocrystal by slurry method (c), ibuprofen-caffeine cocrystal by solvent evaporation method (d)

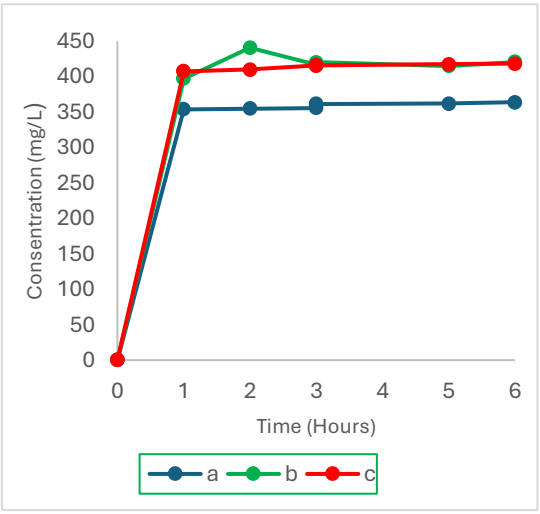

Figure 4. Solubility profile of ibuprofen (a), ibuprofen-

possible formation of an incomplete cocrystal phase or the presence of residual starting components. In contrast, in the solvent evaporation method, particles are able to precipitate and arrange more regularly during the evaporation process, producing sharper diffraction peaks that reflect the formation of a more homogeneous and well-defined cocrystal phase. The difference in results between cocrystals made by the slurry method and solvent evaporation is due to the incongruent solubility of ibuprofen and caffeine in ethanol. Ibuprofen is readily soluble in ethanol (1:1.5), whereas caffeine is considerably less soluble, with a solubility of 1:66 in ethanol [21]. Cocrystal formation between two components with incongruent solubility in a solvent will be difficult to form, because as the amount of solvent decreases during the evaporation process, the component with lower solubility will precipitate [22]. Cocrystal formation between two components with incongruent solubility will be easier to form using the slurry method, which involves adding the component with lower solubility to a saturated or near-saturated solution of the other component [23].

CONCLUSION

The conclusion of this study is that ibuprofen cocrystals can be formed with the coformer caffeine at a molar ratio of 1:1 using the slurry method and solvent evaporation

CONFLICT OF INTEREST

This research has no conflict of interest.

ACKNOWLEDGEMENT

This research was funded through the 2025 Research Group Grant by the Institute of Research and Community Service University of Jember.

REFERENCES

[1] Wisudyaningsih B, Ameliana L. Effect of gelling agent and penetration enhancer on the release rate of ibuprofen-PEG 6000 solid dispersion from gel preparations. *Pharm Educ.* 2022;22(2):55–59. https://doi.org/10.46542/pe.2022.222.5559
[2] Yuliandra, Y., Zaini, E., Syofyan, S., Pratiwi, W., Putri, L.N., Pratiwi, Y.S., Arifin, H. Cocrystal of Ibuprofen–Nicotinamide: Solid-State Characterization and In Vivo Analgesic Activity Evaluation. Sci. Pharm. 2018;86 (23):2-11. https://doi.org/10.3390/scipharm86020023
[3] Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today. 2007;12(23–24):1068–75.
[4] Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins: basic science and product development. J Pharm Pharmacol. 2010;62(11):1607–21.
[5] Serajuddin AT. Salt formation to improve drug solubility. Adv Drug Deliv Rev. 2007;59(7):603–16.
[6] Thakuria R, Delori A, Jones W, Lipert MP, Roy L, Rodriguez-Hornedo N. Pharmaceutical Cocrystals and Poorly Soluble Drugs. Int J Pharm. 2013; 453(1):101-25. https://doi.org/10.1016/j.ijpharm.2012.10.043
[7] Pandey J, Prajapati P, Shimpi MR, Tandon P, Velaga SP, Srivastava A, et al. Studies of Molecular Structure, Hydrogen Bonding and Chemical Activity of a Nitrofurantoin-L-Proline Cocrystal: a Combined Spectroscopy and Quantum Chemical Approach. RSC Adv. 2016 ;6: 74135–54. https://doi.org/10.1039/C6RA13035F
[8] Bučar D-K, Henry RF, Lou X, Duerst RW, Borchardt TB, MacGillivray LR, et al. Cocrystals of caffeine and hydroxy-2-naphthoic acids: Unusual formation of the carboxylic acid dimer in the presence of a heterosynthon. Molecular pharmaceutics. 2007;4(3):339–46. https://doi.org/10.1021/mp070004b
[9] Barikah, K.Z., Yudi, W., Budipratiwi, W. Quercetin-Glycolic Acid Cocrystalization Using Solvent Evaporation and Slurry Methods. Indonesian Journal of Pharmaceutical Science and Technology. 2024; 11(3):305-312. https://doi.org/10.24198/ijpst.v11i3.43596
[10] Patil A, Biradar S, Khandagale N, Zambre V. Formulation and evaluation of fexofenadine hydrochloride–nutraceutical cocrystal to improve bioavailability through inhibition of P-glycoprotein mediated drug efflux. *Int J Drug Deliv Technol.* 2025;15(2):804-11

[11] Mugwiza E, Hahirwa I, Umumararungu T. A UV spectrophotometric method for simultaneous determination of ibuprofen and paracetamol concentration in suspensions. *Rwanda Med J*. 2023;80(3):49–56. doi:10.4314/rmj.v80i3.7
[12] Bashyal, S. Ibuprofen And Its Different Analytical And Manufacturing Methods: A Review. Asian Journal of Pharmaceutical and Clinical Research. 2018; 11(7):25-29. https://doi.org/10.22159/AJPCR.2018.V11I7.24484
[13] The United States Pharmacopeia, USP 30 The National Formulary, NF 25. Rockville: United States Pharmacopeial Convention, Inc.; 2007.
[14] Schultheiss, N., Newman, A. Pharmaceutical Cocrystals and Their Physicochemical Properties. Crystal Growth and Design. 2009; Vol.9 (6):2950-67. https://doi.org/10.1021/cg900129f
[15] Qiao, N., Li, M., Schlindwein, W., Malek, N.,Davies, A., Trappitt, G. Pharmaceutical Cocrystals: An Overview. International Journal of Pharmaceutics. 2011; Vol 419:1-11. https://doi.org/10.1016/j.ijpharm.2011.07.037
[16] Setyawan D, Sari R, Yusuf H, Primaharinastiti R. Preparation and characterization of artesunate–nicotinamide cocrystal by solvent evaporation and slurry method. *Asian J Pharm Clin Res*. 2014;7(1):62–5.
[17] Yuliandra Y, Zaini E, Syofyan S, Pratiwi W, Putri LN, Pratiwi YS, Arifin H. Cocrystal of ibuprofen–nicotinamide: solid-state characterization and in vivo analgesic activity evaluation. *Sci Pharm*. 2018;86(2):23. https://doi.org/10.3390/scipharm86020023
[18] United States Pharmacopeia (2018). *Monographs, Caffeine*. FCC. Rockville, MD: United States Pharmacopeia.
[19] Alatas, F., Sundani, S., Lucy, S., Ismunandar, Hidero, U. Cocrystal Formation Between Didanosine and Two Aromatic Acids. International Journal of Pharmacy and Pharmaceutical Sciences. 2013; 5(3):275-280.
[20] Sanphui, P. et al. Fast dissolving curcumin cocrystal. Crystal Growth and Design. 2011; 11(9):4135–4145. https://doi.org/10.1021/cg200704s
[21] Galichet, L., Moffat, A., Osselton, M., Widdop, B. Clarke's Analysis of Drugs and Poisons. London: Pharmaceutical Press; 2005.
[22] Friscic T, Jones W. Recent Advances in Understanding the Mechanism of Cocrystal Formation via Grinding. Cryst Growth Des. 2009;9(3):1621-37. https://doi.org/10.1021/cg800764n
[23] Child SL, Rodriguez Hornedo N, Sreenivas L, Jayasankar A, Maheshwari C, McCausland L, et al. Screening Strategies Based on Solubility and Solution Composition Generate Pharmaceutically Acceptable Cocrystals of Carbamazepine. Cryst Eng Comm. 2008;10(7): 856-864. https://doi.org/10.1039/B715396A

Copyright © 2026 The author(s). You are free to share (copy and redistribute the material in any medium or format) and adapt (remix, transform, and build upon the material for any purpose, even commercially) under the following terms: Attribution — You must give appropriate credit, provide a link to the license, and indicate if changes were made. You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use; ShareAlike — If you remix, transform, or build upon the material, you must distribute your contributions under the same license as the original (https://creativecommons.org/licenses/by-sa/4.0/)