International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 5, May 2026 ijppr.humanjournals.com ISSN: 2349-7203

Advances in Pharmaceutical Co-Crystals: Preparation Methods, Characterization Techniques, and Therapeutic Applications

P Deepika, Dr. Devi Dhamayanthi, Diven B Chajjer, R J Nivethitha, M Ahrsiya Noorin, Dr. Daisy Chellakumari

Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai-03 India.

Received: 30 March 2026 Revised: 25 April 2026 Accepted: 30 April 2026

ABSTRACT

Pharmaceutical co-crystals are innovative multi-component crystalline solids formed by active pharmaceutical ingredients (APIs) and co-formers through non-covalent interactions such as hydrogen bonding, van der Waals forces, and π–π stacking. Drug–drug co-crystals (DDCs) offer a promising approach to enhance solubility, dissolution rate, permeability, stability, bioavailability, and tabletability without altering the intrinsic pharmacological activity of the parent drugs. This review provides a comprehensive overview of the physicochemical properties of co-crystals, their classification, and the mechanisms underlying their formation. Various preparation methods including solution-based, solid-state, melt-assisted, and advanced emerging techniques are discussed with emphasis on scalability and pharmaceutical applicability. Case studies highlight successful co-crystal systems that improve therapeutic performance across diverse therapeutic areas. Furthermore, characterization techniques such as X-ray diffraction, DSC/TGA, FTIR, Raman spectroscopy, and solid-state NMR are explored to validate co-crystal formation and structural integrity. Applications in oncology, cardiovascular, anti-inflammatory, and infectious disease therapies demonstrate the potential of co-crystals as a versatile platform for fixed-dose combinations and patient-centric drug delivery. The review concludes with challenges and future perspectives in co-crystal development, regulatory acceptance, and industrial translation.

Keywords: Advances in Pharmaceutical Co-Crystals, Preparation Methods, Characterization Techniques, Therapeutic Applications

1. Introduction to co-crystals

Pharmaceutical co-crystals are multi-component crystalline solids consisting of an active pharmaceutical ingredient (API) and one or more stoichiometric co-formers joined by noncovalent interactions such as hydrogen bonds, van der Waals forces, and π–π stacking. Because at least one coformer is another therapeutically active drug, drug–drug co-crystals (DDCs) enable fixed-dose combos or synergistic therapy without covalent chemical alteration [1]. Cocrystallization is considered a "green" solid-state method that improves significant physicochemical properties such solubility, dissolution rate, permeability, stability, and tabletability without altering the intrinsic pharmacological action of the parent drugs. When co-crystallized with suitable co-formers, co-crystal can significantly increase the apparent solubility and oral bioavailability of weakly water-soluble BCS class II and III, as demonstrated for several model APIs (such as 5-fluorouracil, ibuprofen, and theophylline).pharmaceuticals[2]. In treatments for cancer, tuberculosis, viral infections, and heart disease, often use several medicines together. If the active ingredients are already approved, co-crystals are usually seen by regulators as new solid forms rather than brand-new drugs. This makes it faster and easier to develop combination medicines [3].

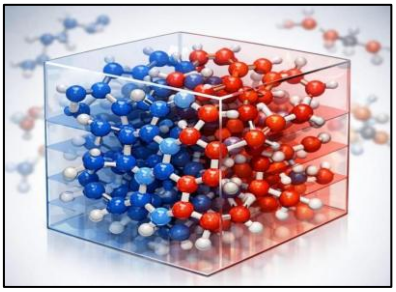


Figure 1: Drug co crystal

2.Physicochemical properties of co crystal

2.1 Melting point

By determining how quickly and over what range a solid melt, the melting point a physical property of solids is used to evaluate the products purity [4]. Selecting a coformer with a higher melting point can improve the thermal stability of an API since high melting points indicate that new materials are thermodynamically stable. Co-crystals with low melting points can be useful when working with thermolabile medications. The most popular techniques for figuring out melting points are Thermogravimetric Analysis (TGA) & Differential Scanning Calorimetry (DSC). By choosing the right co-formers, medicinal co-crystals' melting point can be raised [5].

2.2 Solubility

The solubility of co-crystals plays a significant role in determining their medicinal properties [10]. Because cocrystals have a higher concentration of free drug that can be absorbed, they are more soluble than drugs. Co crystallization is one of the many methods employed by researchers to make drugs more soluble. Other methods include solid dispersion and salt formation. A cocrystal will be less soluble than the original material because of the altered underlying crystal structure. Most studies offer information on powder dissolving throughout a range of time periods [11].

2.3 Stability

When developing novel dosage formulations, stability research is essential. To determine the effect of water on the formulation, automated water sorption/desorption tests are performed under relative humidity stress. Several researchers have examined co-crystal behaviour under relative humidity stress conditions [12,13]. Indomethacin-saccharin co-crystals showed low water sorption during relative humidity tests, and under experimental conditions, no dissociation or transformation occurred [12]. At different relative humidity levels (0%, 43%, 75%, and 98%) across different time periods (one day, three days, one week, and seven weeks), theophylline co-crystals displayed relative humidity stability behaviour. The results showed improved stability and physical characteristics, especially by avoiding hydrate formation [13]. The chemical stability analysis should look at any changes or deterioration in the formulation, mainly under accelerated stability circumstances. Over a two-month period at different temperatures, glutaric co-crystals containing an API demonstrated exceptional chemical stability [14].

2.4 Bioavailability

The degree to which a material or medication becomes completely accessible to its intended biological target is known as bioavailability. One major challenge in developing new formulations is the low oral bioavailability of APIs [15].After oral administration of the original form and then the cocrystal, the amount of drug in the blood is measured.[11] Another example is the formation of co-crystals with nicotinamide, which improved baicalein's oral bioavailability. When compared to the pure drug in rats, this augmentation produced peak plasma concentration (C_{max}) and area under the curve (AUC) that were 2.49 and 2.80 times greater, respectively [16]. Co-crystals of meloxicam and aspirin showed improved oral bioavailability and a 12-fold quicker onset of action in rats as compared to the pure drug [17Furthermore, co-crystals of 6-mercaptopurine, a BCS class-II medicine, showed a greater oral bioavailability of 168.7% in rats when compared to the pure drug [18].

2.6 Permeability

The n-octanol/water partition coefficient, which may be computed using log P and (C log P) for unaltered drug forms, is the main indicator of drug permeability. One of the most important aspects of drug absorption and distribution is drug accessibility via the cellular membrane [2].

2.7 Tabletability

Tabletability, compaction, and crystal packing all important aspects of formulation research may be affected by the co-crystallization of the drug and coformer. It was discovered that the compaction behaviour of paracetamol co-crystals with trimethyl glycine and oxalic acid was superior to that of the drug alone [20]. Co-crystallization of resveratrol with isoniazid and 4aminobenzamide was found to significantly increase tabletability [21]. The mechanical properties of APIs, such as co-crystals of vanillin isomers, can be altered by altering the crystal packing during co-crystallization [22]. The mechanical characteristics are improved when isoniazid co-crystallizes with other co-formers, according to our previous research [23].

2.8 Hygroscopicity

A medication ingredient's hygroscopicity needs to be carefully investigated because it can have an impact on its physicochemical characteristics, including solubility, dissolving rate, stability, bioavailability, and mechanical properties. Thus, preserving the hygroscopic stability of the anhydrate form is one of the most challenging parts of drug development. This problem has been addressed in a number of ways, such as adding suitable excipients to the formulation, employing suitable packing to minimize moisture absorption, and coating the drug product with enteric polymers.[24]

3. Classification of Co-Crystals [25]

Binary Co-Crystals	Composed of two components, typically an active pharmaceutical ingredient (API) and a co-former, in a defined stoichiometric ratio.
Ternary/Quaternary Co-Crystals	Consist of three or four different components arranged in a specific stoichiometric proportion within a single crystal lattice.
Polymorphic Co-Crystals	Co-crystals that exist in multiple crystalline forms, exhibiting different packing arrangements and physicochemical properties.
Salt Co-Crystals	Hybrid systems involving both ionic (salt-like) and neutral interactions, acting as an intermediate between salts and cocrystals.
Solvated/Hydrated Co-Crystals	Contain solvent molecules (solvates) or water (hydrates) incorporated into the crystal lattice.
Other Outcomes	Non-co-crystalline forms such as eutectic mixtures, amorphous or gel-like systems, solid dispersions, and ionic liquids that may arise during co-crystallization attempts.

4. Mechanism of co-crystal formation

During co-crystallization, which is governed by crystal engineering principles, complementary functional groups of the API and coformer (such as carboxylic acid–pyridine, carboxylic acid– amide, and amide–amide) produce stable supramolecular synthons through directional hydrogen bonding. These synthons homosynthons within the same molecule or heterosynthons between API and coformer determine the packing pattern in the crystal lattice, which ultimately influences bulk properties including melting temperature, solubility, and mechanical strength (26).

Co-crystallization is driven at the molecular level by optimized non-covalent interactions that reduce lattice energy. Strong hydrogen-bond donors and acceptors in both components frequently favour stable co-crystal formation, however steric hindrance or mismatched pKa values may promote phase separation or stable polymorphs of the individual medications (27).

Co-crystals are created through solution-mediated processes when the API and coformer dissolve in a common solvent and then nucleate as a new thermodynamically stable (or metastable) phase, often via a supersaturated state. In solid-state methods (such as grinding), co-crystallization occurs through mechanical activation, where local pressure and shear break crystal lattices, allowing for close mixing and the formation of new intermolecular connections at the interface (24).

5. Methods of preparation of drug–drug co-crystals

Co-crystal formation can be achieved via a variety of solid-state and solution-based techniques, each having special advantages in terms of solvent use, polymorphism control, and scale-up. The choice of method for drug co-crystals (DDCs) is influenced by the solubility profile, stoichiometric ratio, API stability, and intended dosage form [29].

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 5, May 2026 ijppr.humanjournals.com ISSN: 2349-7203

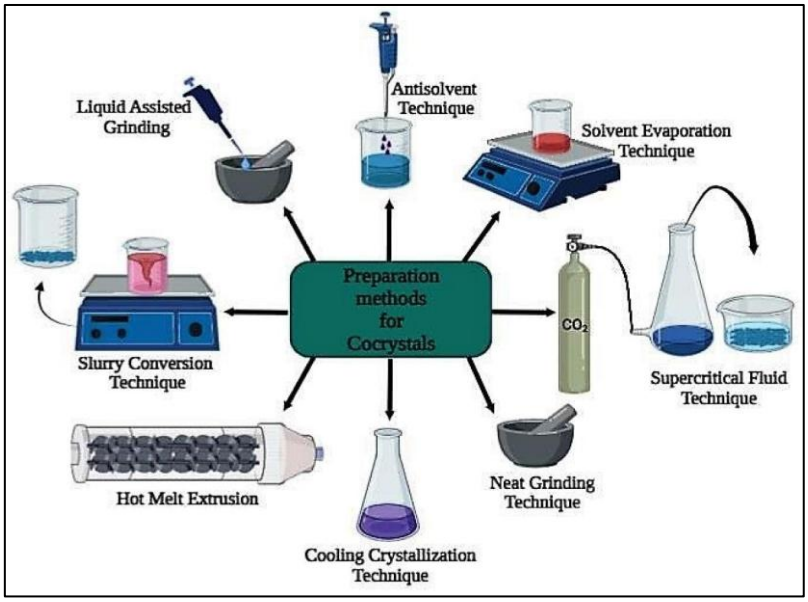


Figure 2 Different Methods of preparation of drug–drug co-crystals

5.1 Solution-based methods

5.1.1. Slow evaporation

The API and the co former are dissolved in a suitable solvent at a present stoichiometric ratio while being magnetically agitated to ensure molecular level mixing. The solution is then kept at a controlled temperature and humidity as the solvent gradually evaporates, allowing the system to reach supersaturation and start the co crystal phase. This method yields high-quality single crystals suitable for Single Crystal X-ray Diffraction (SCXRD) and in-depth structural analysis, despite being time-consuming and difficult to scale for commercial production.(27)

5.1.2. Cooling crystallization

A heated, saturated solution of Drug and Co former is made, and it is then gradually cooled (usually under controlled ramping, e.g., 0.1 - 1 °C/min) to induce co-crystallization. The cooling rate has a significant effect on nucleation kinetics, polymorphism purity, and crystal size. Slower cooling encourages larger crystals with fewer defects, but faster cooling may result in tiny particles or metastable forms that require additional recrystallization or grinding.(30)

5.1.3. Antisolvent (miscible solvent) method

The drug solution is rapidly mixed into with a miscible antisolvent (such as water added to an ethanol solution) to significantly reduce solubility and induce immediate co-crystallization. This technique is commonly used to create micro or nanosized cocrystal , which can enhance solubility and bioavailability when added to tablets or capsules. Temperature, solvent/antisolvent ratio, and mixing strength must be carefully controlled to avoid phase separation or amorphous byproducts.(29)

5.1.4. Slurry conversion

The API and co former are suspended in a solvent in which at least one component is partially soluble to generate a slurry that is shake for several hours to days. Over time, the more thermodynamically stable co crystal phase gradually replaces the surplus solids in a pseudoequilibrium process. Slurry conversion is advantageous for purification and scale up because it can selectively favour the chosen co-crystal polymorph and removes the need for both medications to entirely dissolve.(29)

5.1.5. Sono-crystallization

Ultrasound is used to create cavitation bubbles in an API and co former solution. These bubbles create localized high pressure and temperature, accelerating nucleation and decreasing crystal size. This method is useful for producing fine, uniform co crystal particles with improved dissolving and can be combined with antisolvent or chilling techniques for increased control.(32)

5.2 Solid-state (mechanochemical) methods

5.2.1. Liquid-assisted grinding (LAG)

A small amount of solvent (a few microliters per milligram of solid) is added during grinding to enhance molecular diffusion without creating a bulk solution. LAG often produces higher co-crystal yields and greater phase purity than neat grinding, and it is commonly used in the initial phases of co-form selection for drug co crystal.(31)

5.2.2. Neat grinding (dry grinding)

Drug and co former powders are mixed in the proper molar ratio and either manually ground in a mortar and pestle or high-energy ball milled. The mechanical energy disrupts crystal lattices, increases molecular mobility at the interface, and forms new hydrogen-bonded networks characteristic of the drug co crystal. This screening technique is simple and solventfree, although it may yield partially amorphous or mixed-phase molecules that require further characterization.(26)

5.2.3. Temperature-controlled grinding and cryo-grinding

Grinding at different temperatures may have an impact on the co-crystals thermodynamic stability compared to the individual drugs. Cryo-grinding is particularly useful for thermally labile APIs where the targeted drug co crystal is prone to desolvation or melting at normal temperature.(4)

5.3 Melt- and thermally assisted methods

5.3.1. Hot-melt extrusion (HME)

Heat and shear are used to melt the API and co former in a twin-screw extruder; the molten phase solidifies and forms a matrix that is drug co crystal containing after cooling. Polymerco-crystal systems, direct formulation into tablets or pellets, and continuous manufacturing can all benefit from HME; however, the processing temperature must be carefully selected in relation to the melting points and glass-transition temperatures of both components.(29)

5.3.2. Cooling-melt co-crystallization

Drugs and co former are totally melted together and then cooled under carefully controlled conditions, such as gradually cooling in a sealed tube or in an inert atmosphere, to produce a co-crystalline solid. This method is suitable for APIs with relatively low melting points and strong heat stability, and it can yield co-crystals that are difficult to extract from solution [30].

5.3.3. Solvent-free mechano-thermal processing

By partially melting at contact sites through controlled heating (mechano-thermal), ball milling can encourage co-crystallization without the need for bulk solvents. This hybrid approach expands the number of viable drug co crystal systems by fusing the advantages of solid-state processing and thermal activation.(24)

5.4 Advanced and emerging techniques

5.4.1. Supercritical fluid (SCF) methods

Supercritical carbon dioxide can be used as an antisolvent (supercritical antisolvent crystallization) or as an atomization medium (supercritical-assisted spray drying) to rapidly precipitate API and co-drug combinations into fine co-crystalline particles. SCF-based techniques are attractive for inhalable or parenteral drug co crystal because they offer good control over residual solvent levels, polymorphic shape, and particle size.(27)

5.4.2. Spray drying and coaxial spray methods

A solution of the two drugs is atomized and rapidly dried, resulting in either co-amorphous or co-crystalline particles, depending on factors (solution concentration, inlet-outlet temperature, feed rate). Coaxial spray techniques have been used to create theophylline-based co-crystals that range in size from micro to nanosized and have finely controlled dissolving behavior.(31)

5.4.3. Freeze-drying and electrospray

Freeze-drying API and co-drug solutions can produce porous, highly soluble co-crystalline or co-amorphous powders suitable for orodispersible or lyophilized dosage forms. Electrospray technique may create tiny co crystal droplets that solidify into nanocrystals with controlled shape for customized delivery systems.(27)

5.4.4. Microwave- and laser-assisted crystallization

Microwave-assisted heating can accelerate co-crystallization in solution or slurry systems and reduce processing times by providing rapid, uniform heating. Laser-induced crystallization has been studied as a highly targeted method to start nucleation in specific regions of a solution or film in order to carefully control the position and size of co-crystals.(30)

5.4.5. 3D-printing of co-crystal-loaded systems

Co-crystals can be integrated into thermoplastic or solvent-cast filaments and then deposited layer by layer using Fused-Deposition Modeling (FDM) or similar 3D printing techniques. This technique allows for patient-specific dosing, complex release features (such delayed or multiphase release), and the combining of many co crystal into a single dose form.[3]

6. Co-crystal Formulations in Recent Studies

API Name	Co-former Name	Result
Modafinil	Sodium acetate (2022)	Enhanced solubility and dissolution (highest performer)[33]
5-Fluorouracil	L-Proline (2022)	Improved permeation (3.89x), bioavailability, and solubility (4.6x). [34]
Roxadustat	Nicotinamide (2023)	Enhanced general physicochemical characteristics and photochemical stability. [35]
Ketoprofen	Fumaric acid (2022)	Improved solubility and anti-inflammatory properties in vivo. [36]
Fluconazole	Benzoic acid (2025)	Better mechanical and flow qualities, a 13x increase in solubility. [37]

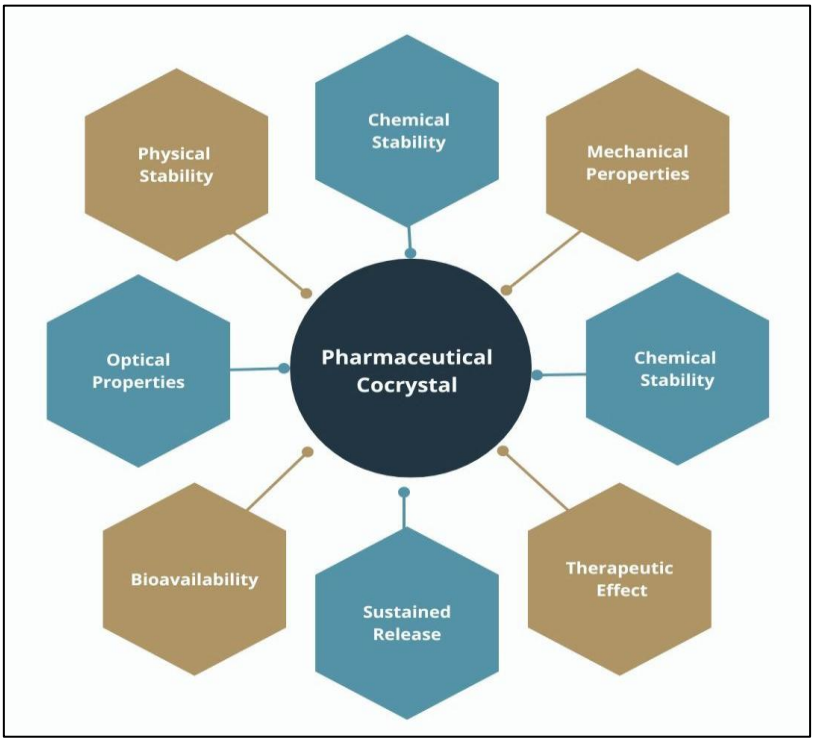
API Name	Co-former Name	Result
Citric acid	Nicotinamide	Enhanced stability hygroscopicity in formulations. [38] and decreased effervescent
Amiodarone HCl	Glutamine, Urea, Citric acid, Ascorbic acid (2020)	Co-crystallization leads to increased solubility. Enhanced in the production of tablets used to improve solubility, solubility and use assessed for improving solubility crystallization. [39] through co-
piroxicam	sucralose	Co-crystals utilized in buccal films have demonstrated improved drug release and bioavailability, as well as six times more solubility. [40]
Curcumin	Ascorbic acid (2020)	Enhanced solubility and antioxidant activity; stable co-crystal formed. [41]
Telmisartan	Hydrochlorothiazide (2023)	Solubility, moisture stability, and bioavailability were all enhanced by drug-drug cocrystals. [42]
Ivermectin	Cinnamic acid (2023)	Enhanced medication release and solubility; prepared into tablets. [43]
RS-Ofloxacin	L-(+)-Tartaric acid (2025)	Increased enantiomeric purity and successful chiral resolution using diastereomeric co-crystal formation. [44]
8-Hydroxyquinoline	Acetone-(2,4-dinitrophenyl)hydrazine (2024)	Creation of a new supramolecular cocrystal with π–π stacking, strong hydrogen bonds, and possible antioxidant properties. [45]

Ketoprofen	p-Aminobenzoic acid (2021)	Better physicochemical characteristics and increased solubility. [46]
5-Fluorouracil	Cinnamic acid	Enhanced anticancer growth inhibition capacity at 100 μgml−1 by 67.30% in comparison to API. [47]

API Name	**Co-former Name**	**Result**
Allopurinol	Piperazine / 2,4-dihydroxybenzoic acid	Compared to API, the ALP-24DHBZA cocrystal's solubility was 50% better and the ALP-PIP cocrystal's diffusion was 41% better after 8 hours. [48]
Sulfathiazole	Amantadine hydrochloride	Improved penetrability by two times and water solubility by 1.83–5.23 times. [49]
Ambrisentan	Syringic acid	1.8 times the intrinsic dissolving rate and 4.8 times the solubility when compared to API. [50]
Berberine chloride	Myricetin	Reduced moisture absorption of 1.5% water up to 95% relative humidity and enhanced hygroscopicity. [51]
Bumetanide	Caprolactam	Enhanced solubility by 1.7 times and intrinsic dissolving rate by 1.4 times in comparison to API. [52]
Donepezil	1,3-Diiodotetrafluorobenzene	Melting point that is 20 °C higher than API 1.6-fold increase in solubility over API. [53]
Ethenzamide	Glutaric acid / malonic acid / maleic acid	Melting point that is 20 °C higher than API 1.6-fold increase in solubility over API. [54]
Ethionamide	Salicylic acid	Increased ETH content in cocrystal form with a dissolving rate of 10 mg L−1. [55]
Famotidine	Theophylline	As opposed to the observed phase shifts of form A famotidine within 1 hour, the cocrystal maintains its original peak position even after 24 hours, indicating improved stability in ph 1.2. [56]
Febuxostat	Piroxicam	2.8 times better dissolution than pure piroxicam and 1.5 times better solubility in ph 6.8 buffer and 1.24 times better solubility in ph 7.4 buffer as compared to pure febuxostat. [57]
API Name	**Co-former Name**	**Result**
Isoniazid	Resveratrol	86 percent less permeability than API. [58]
Itraconazole	Suberic acid	39-fold improvements in dissolving performance over API. [59]
Urea	Various organic co-formers (not specified in snippet)	Depending on the type of co-former, many urea co-crystals with enhanced physicochemical characteristics can form. [60]
Rivaroxaban	Niacinamide	Co-crystals with molar ratios of 1:1 and 1:2 enhanced compressibility and flowability upon excipient addition; appropriate for direct compression. [61]
Daidzein	Piperazine	When compared to the parent drug, the daidzein–piperazine co-crystal's formation greatly increased stability, solubility (up to 60.8× in various conditions), permeability (4.8×), and bioavailability (3.2×). [62]
Formononetin	Imidazole	In comparison to pure FMN, the FMN– IMD co-crystal exhibited good physical stability over a 6-month period, as well as 2–3× higher solubility, 4.93× increase in Cmax, and 3.58× increase in AUC. [63]
Ibuprofen (IBF)	Nicotinamide (NA)	FT-IR spectroscopy revealed the formation of an IBF/NA cocrystal; the reaction rate was highly reliant on humidity; the solubility and bioavailability were enhanced. [64]

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 5, May 2026 ijppr.humanjournals.com ISSN: 2349-7203

7.Application of Pharmaceutical co crystals



8. Characterization of co-crystal

Characterization of newly generated cocrystals is an important step in validating cocrystallization. Various techniques have been employed to characterize pharmaceutical cocrystals and elucidate intermolecular interactions.

8.1 Single-crystal and Powder X-ray diffraction (XRD)

The crystalline state of cocrystals can be find out by powder X-ray diffraction (PXRD) and single crystal X-ray diffraction (SCXRD). On the other hand, SCXRD provides accurate structural data, including lattice parameters, space groups, miller indices, unit cell volume, crystal system, and intramolecular and intermolecular interactions. Because cocrystals exhibit unique, sharp peaks that are different from the peaks of the cocrystal components, PXRD can provide information about solid phase crystallinity.[65] Pardela et al. reported using PXRD to quantify cocrystals in the crystalline mixture. They created and applied PXRD to study the mechanochemical production of indomethacin-saccharin cocrystals.[66]

8.3 Thermal Gravimetry Method:

This technique is helpful for figuring out the sample weight when the temperature is changing for a given amount of time. Differential scanning calorimetry (DSC): The presence of an exothermic crest followed by an endothermic crest in the DSC spectra indicates the presence of cocrystal formation. The presence of crest (peaks) in the compound determines the cocrystal formation. Additionally, it can be used to confirm a compound's or molecule's melting point, polymorphic nature, glass temperature, heat of fusion, and exothermic or endothermic behavior. The precise drying temperature for each of the components reaction stages is provided by thermogravimetric analysis. This technique is used to identify the volatile component, determine if crystals are hydrated or solvated, and analyzing decomposition or sublimation from cocrystals Thermal gravimetry can be used to predict crystal purity, solvates/hydrates forms of cocrystals, thermal stability, and compatibility [71].

8.3.1 Differential scanning calorimetry (DSC)

A simple and practical technique for characterizing co-crystals is differential scanning calorimetry [67]. When compared to pure components, co-crystals show a notable shift in their endothermic and exothermic peaks. Co-crystals can be screened by looking at the DSC peak of the physical mixture of co-crystal components [69]. The co-crystal DSC peak is located between the peaks of pure co-crystal components DSC peaks [68]. Nonetheless, there are many examples of co-crystals that have been formulated that have

DSC peaks outside of the API and co-former range. DSC is a very quick and effective approach for the characterisation of cocrystals. It conducts a characterisation analysis using a very little amount of solvent-free sample [70]. The choice of coformer and the conformation of co-crystals require more investigation and data gathering. Additionally, since the heat energy of co-crystals tends to decrease when compared to consumed API, the heat energy reading can also be used for the conformation of formulated co-crystals.[70]

8.4 Spectroscopy characterization

There are two primary categories of co-crystal spectroscopy characterization. Vibrational spectroscopy comes first, followed by nuclear magnetic resonance spectroscopy. Raman and Fourier transform infrared spectroscopy (FTIR) spectroscopy are two subcategories of the vibrational spectroscopic approach. Raman spectroscopy operates on the scattering mechanism of spectroscopy, while infrared spectroscopy operates on the absorption mechanism. A very effective technique for gathering comprehensive structural data about multicomponent systems is NMR spectroscopy.

8.4.1 FTIR spectroscopy

One extremely effective method for determining the production of co-crystals is Fourier transform infrared spectroscopy . A shift in vibrational energy peaks in spectra, mostly as a result of hydrogen bonding forming in the functional group of co-crystal components, confirms the creation of co-crystals. To identify co-crystal formation and provide structural clarification, the FTIR spectra of pure co-crystal components and formed co-crystals are compared [72].

Harry G. Brittain used FTIR spectroscopy to examine co-crystals of cinchona alkaloid-5 nitro barbituric acid. Variations in co-crystal and co-crystal component absorption spectra are noted in the study [73].

8.4.2. Raman spectroscopy

Raman spectroscopy is an in-situ monitoring and characterisation technique for confirming cocrystal formation [74,75]. The FTIR approach is less accurate, precise, and sensitive than Raman spectroscopy. Co-crystal and ionic forms of multi-component systems can be distinguished using Raman spectroscopy. Comparing the change in co-crystal oscillation to that of co-crystal components allows for the evaluation of co-crystal creation [75,76]. Potential uses of Raman spectroscopy in identifying the co-crystal formation of nitrofurantoin and four aminobenzoic acid co-crystal components were shown by Yong Du and colleagues. Raman spectroscopy data can be used to distinguish between various multi-component pharmaceutical molecular solid systems [75]. In order to distinguish between raw ibuprofen and nicotinamide in the physical combination, co-crystals, and residual coformer in the finished product, K. C. Mullers et al. used color coding for fixed crystal patterns. A final product's Raman spectroscopic color-coded image reveals the presence of produced co-crystals and some residual coformer, but there is no indication that pure ibuprofen is present [32].

8.4.3. NMR spectroscopy

Detailed structural information regarding chemical and medicinal co-crystals may be obtained using solid-state NMR spectroscopy. Compared to vibrational spectroscopy and PXRD techniques, Solid-state nuclear magnetic resonance (ssNMR) offers richer information content and high-yield data. Because (ssNMR) is a nondestructive technique, very few samples are needed to acquire data. In order to comprehend the capabilities of (ssNMR), Frederica G. Vogt [32] and colleagues investigated a number of chemical compounds and co-crystals. This work assesses (ssNMR) capacity to monitor structural elements such hydrogen bonding and demonstrate molecular connection [19,28]. The potential of the dynamic nuclear polarization enhanced (ssNMR) approach for the characterisation of co-crystals and salt forms was shown by Li Zhao and colleagues. The H–N bond lengths and 1H–15 N dipolar coupling constants were also more precisely determined by NMR spectroscopy. These criteria allow for the final differentiation of multicomponent systems as co-crystals or salts and the unambiguous assignment of nitrogen protonation states. This technique can also resolve significant ambiguity over the final product's confirmation as salts or co-crystals [19].

REFERENCES

1. Malthankar AS, Jadhav MP, Madhuri D. A brief review on pharmaceutical co-crystals. Int J Creat Res Thoughts. 2021;9(7):e372-e373.
2. Chettri A, Subba A, Singh GP, Bag PP. Pharmaceutical cocrystals: a green way to enhance drug stability and solubility for improved therapeutic efficacy. J Pharm Pharmacol. 2024;76(1):1-12. doi:10.1093/jpp/rgad097.
3. Marcos Valdez MM, Sperandeo NR, Bueno MS, Garnero C. Pharmaceutical cocrystals in drug-delivery technologies: advances from rational design to therapeutic applications. Pharmaceutics. 2026;18(1):128. doi:10.3390/pharmaceutics18010128.

4. Marcos Valdez MM, Sperandeo NR, Bueno MS, Garnero C, Abourahma H, Cocuzza DS, et al. Pyrazinamide cocrystals and the search for polymorphs. CrystEngComm. 2011;13:6442-50. doi:10.1039/c1ce05598d.
5. Ross SA, Lamprou DA, Douroumis D. Engineering and manufacturing of pharmaceutical co-crystals: a review of solvent-free manufacturing technologies. Chem Commun (Camb). 2016;52:8772-86. doi:10.1039/c6cc01289b.
6. Stanton MK, Bak A. Physicochemical properties of pharmaceutical co-crystals: a case study of ten AMG 517 co-crystals. Cryst Growth Des. 2008;8:3856-62. doi:10.1021/cg800173d.
7. Aakeröy CB, Forbes S, Desper J. Using cocrystals to systematically modulate aqueous solubility and melting behavior of an anticancer drug. J Am Chem Soc. 2009;131:17048-9. doi:10.1021/ja907674c.
8. Walsh RDB, Bradner MW, Fleischman S, et al. Crystal engineering of the composition of pharmaceutical phases. Chem Commun (Camb). 2003;(2):186-7. doi:10.1039/b208574g.
9. Bag PP, Reddy CM. Tramadol hydrochloride and its acetonitrile solvate: crystal structure analysis and thermal studies. Proc Natl Acad Sci India Sect A Phys Sci. 2014;84:235-42. doi:10.1007/s40010-013-0118-0.
10. Thenge R, Adhao V, Mehetre G, Chopade N, Chinchole P, Popat R, et al. Modification of physicochemical properties of active pharmaceutical ingredient by pharmaceutical co-crystals. Drug Formulation Design. 2023. doi:10.5772/intechopen.110129.
11. Sarkar M, Borah R, Das R, Ghosh P, Sharma C, Mohanty JP. Pharmaceutical cocrystals: a review on its physico-chemical properties and role in the management of cancer. [Journal/volume/pages incomplete].
12. Basavoju S, Boström D, Velaga SP. Indomethacin-saccharin cocrystal: design, synthesis and preliminary pharmaceutical characterization. Pharm Res. 2008;25:530-41. doi:10.1007/s11095-007-9394-1.
13. Trask AV, Motherwell WDS, Jones W. Physical stability enhancement of theophylline via cocrystallization. Int J Pharm. 2006;320:114-23. doi:10.1016/j.ijpharm.2006.04.018.
14. McNamara DP, Childs SL, Giordano J, et al. Use of a glutaric acid cocrystal to improve oral bioavailability of a low solubility API. Pharm Res. 2006;23:1888-97. doi:10.1007/s11095-006-9032-3.
15. Kumar AR, Saloni J, Kumar D, Lal S, Sharma S. An overview on pharmaceutical cocrystals. Asian J Pharm Res Dev. 2019;7(2):39-46. doi:10.22270/ajprd.v7i2.483.
16. Huang Y, Zhang B, Gao Y, et al. Baicalein-nicotinamide cocrystal with enhanced solubility, dissolution, and oral bioavailability. J Pharm Sci. 2014;103:2330-7. doi:10.1002/jps.24048.
17. Cheney ML, Weyna DR, Shan N, et al. Coformer selection in pharmaceutical cocrystal development: a case study of a meloxicam aspirin cocrystal that exhibits enhanced solubility and pharmacokinetics. J Pharm Sci. 2011;100:2172-81. doi:10.1002/jps.22434.
18. Wang JR, Yu X, Zhou C, et al. Improving the dissolution and bioavailability of 6mercaptopurine via co-crystallization with isonicotinamide. Bioorg Med Chem Lett. 2015;25:1036-9. doi:10.1016/j.bmcl.2015.01.021.
19. Hanrahan MP, Zhao P, Chakravarty A, DiPasquale AG, Sirois LE, Nagapudi K, et al. Characterization of pharmaceutical cocrystals and salts by dynamic nuclear polarization-enhanced solid-state NMR spectroscopy. Cryst Growth Des. 2018;18(4):2109-17.
20. Maeno Y, Fukami T, Kawahata M, et al. Novel pharmaceutical cocrystal consisting of paracetamol and trimethylglycine, a new promising cocrystal former. Int J Pharm. 2014;473:179-86. doi:10.1016/j.ijpharm.2014.07.008.
21. Zhou Z, Li W, Sun WJ, et al. Resveratrol cocrystals with enhanced solubility and tabletability. Int J Pharm. 2016;509:391-9. doi:10.1016/j.ijpharm.2016.06.006.
22. Krishna GR, Shi L, Bag PP, et al. Correlation among crystal structure, mechanical behavior, and tabletability in the co-crystals of vanillin isomers. Cryst Growth Des. 2015;15:1827-32. doi:10.1021/cg5018642.
23. Bag PP. Introduction of plasticity to change mechanical behaviour of pharmaceutical crystals by co-crystallization: a solution of long standing problem in isoniazid. Eng Sci. 2021;15:129-37. doi:10.30919/es8d1501.
24. Guo M, Sun X, Chen J, Cai T. Pharmaceutical cocrystals: a review of preparations, physicochemical properties and applications. Acta Pharm Sin B. 2021;11:2537-64. doi:10.1016/j.apsb.2021.03.030.
25. Patel N, Patani P, Paroha S. Pharmaceutical co-crystals: a novel strategy for enhancing drug performance. Int J Pharm Sci Rev Res. 2019;58(2):150-5.
26. Yadav S, Agnihotri J, Parab I. Co-crystal: an overview on the novel techniques for the formation of cocrystal and its potential benefit in the pharmaceutical industry. World J Pharm Res. 2018;7(10):305-20.
27. Karimi-Jafari M, Padrela L, Walker GM, Croker DM. Creating cocrystals: a review of pharmaceutical cocrystal preparation routes and applications. Cryst Growth Des. 2018;18(10):6370-87. doi:10.1021/acs.cgd.8b00933.
28. Peach AA, Hirsh DA, Holmes ST, Schurko RW. Mechanochemical syntheses and 35Cl solid-state NMR characterization of fluoxetine HCl cocrystals. CrystEngComm. 2018;20(20):2780-92.
29. Jadhav ND, Khandave PS, Jadhav KR, Bachhav RS. Co-crystal: a review on techniques and characterization. Asian J Pharm Res Dev. 2017;5(3):1-6.
30. Zilpe RD, Mulla JAS. Pharmaceutical co-crystals: a concise review on traditional and novel techniques for preparation, their physiochemical properties and applications. Int J Novel Drug Deliv. 2023;15(3):109-21. doi:10.25258/ijndd.v15i3.16778.
31. Barikah KZ. Traditional and novel methods for cocrystal formation: a mini review. Syst Rev Pharm. 2018;9(1):79-82. doi:10.5530/srp.2018.1.15.

32. Silva Filho SF, Pereira AC, Sarraguça JMG, Sarraguça MC, Lopes J, Façanha Filho PF, et al. Synthesis of a glibenclamide cocrystal: full spectroscopic and thermal characterization. J Pharm Sci. 2018;107(6):1597-604. doi:10.1016/j.xphs.2018.01.029.
33. Kumar R, Sheela MA, Sachdeva M. Formulation and evaluation of orodispersible tablets containing co-crystals of modafinil. J Drug Deliv Ther. 2022;12(5-S):829-36. doi:10.22270/jddt.v12i5-s.5634.
34. Yu YM, Liu L, Bu FZ, Li YT, Yan CW, Wu ZY. A novice cocrystal nanomicelle formulation of 5-fluorouracil with proline: the design, self-assembly and in vitro/vivo biopharmaceutical characteristics. Int J Pharm. 2022;617:121635. doi:10.1016/j.ijpharm.2022.121635.
35. Muthusamy AR, Singh A, Sundaram MSS, Wagh Y, Jegorov A, Jain AK. In-silico aided screening and characterization results in stability enhanced novel roxadustat co-crystal. J Pharm Sci. 2024;113:1190-201. doi:10.1016/j.xphs.2023.10.024.
36. Devi S, Kumar A, Kapoor A, Verma V, Yadav S, Bhatia M. Ketoprofen-FA co-crystal: in vitro and in vivo investigation for the solubility enhancement of drug by design of expert. AAPS PharmSciTech. 2022;23:104. doi:10.1208/s12249-022-02253-5.
37. Rathi R, Singh I, Sangnim T, Huanbutta K. Development and evaluation of fluconazole co crystal for improved solubility and mechanical properties. Pharmaceutics. 2025;17(3):371. doi:10.3390/pharmaceutics17030371.
38. Pagire SK, Seaton CC, Paradkar A. Improving stability of effervescent products by cocrystal formation: a novel application of crystal engineered citric acid. Cryst Growth Des. 2020;20:4839-44. doi:10.1021/acs.cgd.0c00616.
39. Patidar VK, Sharma A. Design, formulation and evaluation of amiodarone HCl cocrystal tablet. Eur J Mol Clin Med. 2021;7(8):2020-8.
40. Ammanage A, Rodriques P, Kempwade A, Hiremath R. Formulation and evaluation of buccal films of piroxicam co-crystals. Futur J Pharm Sci. 2020;6:69. doi:10.1186/s43094-020-00033-1.
41. Pantwalawalkar J, More H, Bhange D, Patil U, Jadhav N. Novel curcumin ascorbic acid cocrystal improved solubility. J Drug Deliv Sci Technol. 2021;61:102233. doi:10.1016/j.jddst.2020.102233.
42. Vyas G, Shah J, Jacob S. DoE implementation for telmisartan and hydrochlorothiazide drug cocrystal synthesis to enhance physicochemical and pharmacokinetic properties. J Appl Pharm Sci. 2023;13:67-76. doi:10.7324/JAPS.2023.90012.
43. Popat Jadhav S, Machhindra Patil D, Devidas Sonawane D, Dilip Patil P, Gorakshanath Ghugarkar P, Saad M, et al. Formulation of tablet of ivermectin co-crystal for enhancement of solubility and other physical properties. J Pharm Negat Results. 2023;14(S01):631-9. doi:10.47750/pnr.2023.14.S01.60.
44. Kaviani R, Jouyban A, Shayanfar A. Chiral resolution of RS-ofloxacin through a novel diastereomeric cocrystal formation with L-glutamic acid by evaporative crystallization and quantification with capillary electrophoresis. Sep Purif Technol. 2024;335:129040. doi:10.1016/j.seppur.2024.129040.
45. Zerrouki K, Bouchene R, Tüzün B, Retailleau P. Novel supramolecular co-crystal of 8hydroxyquinoline with acetone-(2,4-dinitrophenyl)hydrazone: one pot synthesis, structural characterization, Hirshfeld surface and energy framework analysis, computational investigation and molecular docking study. J Mol Struct. 2024;1300:137290. doi:10.1016/j.molstruc.2023.137290.
46. Bhatia M, Kumar A, Kumar V, Devi S. Development of ketoprofen-p-aminobenzoic acid co crystal: formulation, characterization, optimization and evaluation. Res Sq. 2021. doi:10.21203/rs.3.rs-596789/v1.
47. Jubeen F, Liaqat A, Amjad F, Sultan M, Iqbal SZ, Sajid I, et al. Synthesis of 5fluorouracil cocrystals with novel organic acids as coformers and anticancer evaluation against HCT-116 colorectal cell lines. Cryst Growth Des. 2020;20(4):2406-14. doi:10.1021/acs.cgd.9b01570.
48. Dai XL, Yao J, Wu C, Deng JH, Mo YH, Lu TB, et al. Solubility and permeability improvement of allopurinol by cocrystallization. Cryst Growth Des. 2020;20:5160-8. doi:10.1021/acs.cgd.0c00326.
49. Wang LY, Bu FZ, Li YT, Wu ZY, Yan CW. A sulfathiazole-amantadine hydrochloride cocrystal: the first codrug simultaneously comprising antiviral and antibacterial components. Cryst Growth Des. 2020;20:2364-72. doi:10.1021/acs.cgd.0c00075.
50. Haneef J, Chadha R. Sustainable synthesis of ambrisentan-syringic acid cocrystal: employing mechanochemistry in the development of novel pharmaceutical solid form. CrystEngComm. 2020;22:2507-16. doi:10.1039/C9CE01818B.
51. Li P, Ramaiah T, Zhang M, Zhang Y, Huang Y, Lou B. Two cocrystals of berberine chloride with myricetin and dihydromyricetin: crystal structures, characterization, and antitumor activities. Cryst Growth Des. 2020;20:157-66. doi:10.1021/acs.cgd.9b00939.
52. Allu S, Bolla G, Tothadi S, Nangia AK. Novel pharmaceutical cocrystals and salts of bumetanide. Cryst Growth Des. 2020;20:793-803. doi:10.1021/acs.cgd.9b01195.
53. Nemec V, Vitasović T, Cinčić D. Halogen-bonded cocrystals of donepezil with perfluorinated diiodobenzenes. CrystEngComm. 2020;22(34):5573-7. doi:10.1039/D0CE01065K.
54. Kozak A, Marek PH, Pindelska E. Structural characterization and pharmaceutical properties of three novel cocrystals of ethenzamide with aliphatic dicarboxylic acids. J Pharm Sci. 2019;108(4):1476-85. doi:10.1016/j.xphs.2018.10.060.
55. Bernasconi D, Bordignon S, Rossi F, Priola E, Nervi C, Gobetto R, et al. Selective synthesis of a salt and a cocrystal of the ethionamide-salicylic acid system. Cryst Growth Des. 2020;20:906-15. doi:10.1021/acs.cgd.9b01299.
56. Saikia B, Sultana N, Kaushik T, Sarma B. Engineering a remedy to improve phase stability of famotidine under physiological pH environments. Cryst Growth Des. 2019;19:6472-81. doi:10.1021/acs.cgd.9b00931.
57. Modani S, Gunnam A, Yadav B, Nangia AK, Shastri NR. Generation and evaluation of pharmacologically relevant drug-drug cocrystal for gout therapy. Cryst Growth Des. 2020;20:3577-83. doi:10.1021/acs.cgd.0c00106.

58. Rosa J, Machado TC, Da Silva AK, Kuminek G, Bortolluzzi AJ, Caon T, et al. Isoniazid resveratrol cocrystal: a novel alternative for topical treatment of cutaneous tuberculosis. Cryst Growth Des. 2019;19:5029-36. doi:10.1021/acs.cgd.9b00313.
59. Weng J, Wong SN, Xu X, Xuan B, Wang C, Chen R, et al. Cocrystal engineering of itraconazole with suberic acid via rotary evaporation and spray drying. Cryst Growth Des. 2019;19:2736-45. doi:10.1021/acs.cgd.8b01873.
60. Eisa M, Brondi M, Williams C, Hejl R, Baltrusaitis J. From urea-to-urea cocrystals: a critical view of conventional and emerging nitrogenous fertilizer materials for improved environmental sustainability. Sustain Chem Environ. 2025;9:100209. doi:10.1016/j.scenv.2025.100209.
61. Solomon C, Sârbu I, Anuța V, Ozon EA, Musuc AM, Fița AC, et al. Preformulation studies of tablets containing rivaroxaban-niacinamide cocrystallization compounds. Farmacia. 2025;73(3):706-12. doi:10.31925/farmacia.2025.3.17.
62. Wang Z, Li S, Li Q, Wang W, Liu M, Yang S, et al. A novel cocrystal of daidzein with piperazine to optimize the solubility, permeability and bioavailability of daidzein. Molecules. 2024;29(8):1710. doi:10.3390/molecules29081710.
63. Kim J, Lim S, Kim M, Ban E, Kim Y, Kim A. Using the cocrystal approach as a promising drug delivery system to enhance the dissolution and bioavailability of formononetin using an imidazole coformer. Pharmaceuticals (Basel). 2024;17(11):1444. doi:10.3390/ph17111444.
64. Ishihara S, Hattori Y, Otsuka M, Sasaki T. Cocrystal formation through solid-state reaction between ibuprofen and nicotinamide revealed using THz and IR spectroscopy with multivariate analysis. Crystals (Basel). 2020;10(9):760. doi:10.3390/cryst10090760.
65. Sathisaran I, Dalvi SV. Engineering cocrystals of poorly water-soluble drugs to enhance dissolution in aqueous medium. Pharmaceutics. 2018;10(3):108.
66. Padrela L, de Azevedo EG, Velaga SP. Powder X-ray diffraction method for the quantification of cocrystals in the crystallization mixture. Drug Dev Ind Pharm. 2012;38(8):923-9.
67. Bruni G, Maggi L, Mustarelli P, Sakaj M, Friuli V, Ferrara C, et al. Enhancing the pharmaceutical behavior of nateglinide by cocrystallization: physicochemical assessment of cocrystal formation and informed use of differential scanning calorimetry for its quantitative characterization. J Pharm Sci. 2019;108(4):1529-37.
68. Schultheiss N, Newman A. Pharmaceutical cocrystals and their role in drug delivery. Cryst Growth Des. 2009;9(6):2950-67.
69. Saganowska P, Wesolowski M. DSC as a screening tool for rapid co-crystal detection in binary mixtures of benzodiazepines with co-formers. J Therm Anal Calorim. 2018;133(1):473-83.
70. Park B, Yoon W, Yun J, Ban E, Yun H, Kim A. Emodin-nicotinamide (1:2) cocrystal identified by thermal screening to improve emodin solubility. Int J Pharm. 2019;557:26-35.
71. Buddhadev SS, Garala KC. Pharmaceutical cocrystals—a review. Sciforum. 2020. [cited from iocc_2020.sciforum.net].
72. Ali HRH, Alhalaweh A, Mendes NFC, Ribeiro-Claro P, Velaga SP. Solid-state vibrational spectroscopic investigation of cocrystals and salt of indomethacin. CrystEngComm. 2012;14(20):6665-74.
73. Brittain HG. Vibrational spectroscopic study of the cocrystal products formed by cinchona alkaloids with 5-nitrobarbituric acid. J Spectrosc. 2015;2015:619174.
74. Du S, Wang Y, Wu S, Yu B, Shi P, Bian L, et al. Two novel cocrystals of lamotrigine with isomeric bipyridines and in situ monitoring of the cocrystallization. Eur J Pharm Sci. 2017;110:19-25.
75. Tanaka R, Hattori Y, Ashizawa K, Otsuka M. Kinetics study of cocrystal formation between indomethacin and saccharin using high-shear granulation with in situ Raman spectroscopy. J Pharm Sci. 2019;108(10):3201-8.
76. Xue Y, Du J, Cai Q, Zhang Q. Spectroscopic investigation on structure and pH dependent cocrystal formation between gamma-aminobutyric acid and benzoic acid. Spectrochim Acta A Mol Biomol Spectrosc. 2018;191:377-81.
77. Silva Filho SF, Pereira AC, Sarraguça JMG, Sarraguça MC, Lopes J, Façanha Filho PF, et al. Synthesis of a glibenclamide cocrystal: full spectroscopic and thermal characterization. J Pharm Sci. 2018;107(6):1597-604. doi:10.1016/j.xphs.2018.01.029.

How to cite this article:
P Deepika et al. Ijppr.Human, 2026; Vol. 32 (5): 482-493.
Conflict of Interest Statement: All authors have nothing else to disclose.