INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

A Review on Pharmaceutical Cocrystals – Preparation, Characteristics and Applications

R. Satya Deepthi*, M. Sunitha Reddy, K. Anie Vijetha

Department of Pharmaceutics, Centre for Pharmaceutical Sciences, UCESTH, Jawaharlal Nehru Technological University, Hyderabad, Kukatpally, Telangana, India 500085

ARTICLE INFO

Published: 15 Aug 2025
Keywords:
Cocrystals, Hydrogen bond, Coformer, Solubility, PXRD, FTIR
DOI:
10.5281/zenodo.16882709

ABSTRACT

Cocrystals are defined as multicomponent crystalline materials composed of an active pharmaceutical ingredient (API) and one or more neutral coformers, held together through non-covalent interactions such as hydrogen bonding, π–π stacking, and van der Waals forces. Unlike salts or solvates, cocrystals retain the chemical identity of the API while offering a unique opportunity to modify its physicochemical properties without altering its pharmacological activity. This makes cocrystal engineering an attractive strategy in pharmaceutical development, particularly for improving drug solubility, dissolution rate, stability, and bioavailability. This review provides a comprehensive overview of the fundamental principles of cocrystal formation, including the selection criteria for suitable coformers and the role of supramolecular synthons in guiding crystal assembly. Various preparation techniques such as solvent evaporation, grinding, and slurry conversion are discussed, highlighting their advantages and limitations. In addition, a range of analytical techniques—including powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), and single-crystal X-ray diffraction (SCXRD)—are examined for their role in characterizing and confirming the formation of cocrystals. Overall, the strategic application of cocrystals represents a significant advancement in formulation science, offering a versatile platform to overcome challenges associated with poorly soluble or unstable drug molecules.

INTRODUCTION

Cocrystals have emerged as a promising and versatile strategy in the pharmaceutical field to enhance the physicochemical properties of active

***Corresponding Author:** R. Satya Deepthi
Address: *Department of Pharmaceutics, Centre for Pharmaceutical Sciences, UCESTH, Jawaharlal Nehru Technological University, Hyderabad, Kukatpally, Telangana, India 500085.*
Email : satyadeepthi.2000@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

pharmaceutical ingredients (APIs) without altering their intrinsic therapeutic activity. Defined as multicomponent crystalline systems composed of two or more neutral molecules in a definite stoichiometric ratio, cocrystals are held together by non-covalent interactions, primarily hydrogen bonds, π–π stacking, and van der Waals forces. These interactions enable the rational design of solid-state forms, providing a platform for modifying properties such as solubility, stability, dissolution rate, and bioavailability—critical attributes in drug development and delivery.

The formation of pharmaceutical cocrystals is based on crystal engineering, which involves understanding and manipulating of intermolecular interactions to achieve desired structural and functional outcomes. A key component in cocrystal design is the selection of a suitable coformer—typically a molecule with generally regarded as safe (GRAS) status—that can reliably and predictably interact with the API through complementary functional groups. These interactions include hydrogen bonding between donor and acceptor sites, π–π interactions among aromatic systems, halogen bonding, and other dipole-based attractions. The predictability of such interactions allows for the construction of supramolecular synthons—recurring structural motifs that guide the self-assembly of molecular components into a stable crystalline lattice.

Hydrogen bonding is the most common and crucial interaction in cocrystal formation, largely due to its directional nature and moderate strength, which provides stability to the resulting crystal. For example, carboxylic acids, amides, alcohols, and ureas present in APIs or coformers can act as hydrogen bond donors or acceptors, facilitating the formation of robust cocrystalline networks. π–π stacking interactions, while generally weaker, also contribute significantly in systems containing aromatic rings, enhancing packing efficiency and stability. Additionally, the incorporation of halogen bonding in cocrystals is gaining attention as a way to engineer specific crystal structures through directional halogen–electron donor interactions.

Beyond the fundamental interactions, cocrystallization offers a means of overcoming formulation challenges such as poor aqueous solubility, low permeability, or polymorphic instability of APIs. The formation of cocrystals does not involve ionic bonding or salt formation, making it particularly advantageous for APIs that are non-ionizable or weakly ionizable. Moreover, cocrystals provide an alternative to other solid forms like salts, solvates, or polymorphs, offering enhanced patentability and regulatory flexibility.

This review aims to comprehensively examine the current landscape of pharmaceutical cocrystals, with an emphasis on the molecular interactions governing API–coformer assembly, strategies for coformer selection, methods of cocrystal preparation, characterization techniques, and recent advancements in the field. By deepening the understanding of how molecular interactions drive cocrystal formation and performance, researchers can better exploit this approach to optimize drug formulations and enable new therapeutic solutions.

SELECTION OF COFORMER:

A significant obstacle to pharmaceutical crystal development is selecting coformers and its compatibility with specific APIs. The selection of a coformer can be carried out using experimental approaches, knowledge-based strategies, or the supramolecular synthon approach.

1. Experimental method for Cocrystal Screening: This approach is primarily based on a trial-and-error strategy. In this method, an active

pharmaceutical ingredient (API) is cocrystallized with empirically selected coformers. The successful formation of cocrystals is then confirmed using analytical techniques such as UV spectroscopy, powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and others.

2. Knowledge-based method: Knowledge-based approaches allow for the selection of appropriate coformers by utilizing factors such as hydrogen bonding patterns, pKa-based predictions, and other molecular interaction models.

3. Hydrogen Bond method: Donohue's Rules for Hydrogen Bonding in Molecular Crystals:

- Complete Utilization of Donors: All available acidic hydrogens (i.e., hydrogen bond donors) in a molecular crystal will participate in hydrogen bonding.
- Maximal Engagement of Acceptors: If hydrogen bond donors are present, all good hydrogen bond acceptors will be involved in hydrogen bonding.
- Selective Interaction**:** Hydrogen bonds are most likely to form between the most favourable hydrogen-bond donor and the most suitable acceptor available.

4. pKa-based method: The difference in pKa values between an acid and a base can help predict whether a salt or a cocrystal will form. The pKa value, which reflects the acid dissociation constant, also influences the oral bioavailability of drugs by affecting their absorption characteristics in the body. The prediction of cocrystal versus salt formation is based on the study of proton transfer, typically evaluated using the ΔpKa value, calculated as:

ΔpKa = [pKa (base)−pKa (acid)].

If ΔpKa (pKa of base – pKa of acid) is **< 0**, cocrystal formation is likely. When ΔpKa is greater than 3, the formation of a salt is generally favoured. For values between 0 and 3, both are possible, and experimental verification is necessary. This method is particularly useful for ionizable APIs and acidic/basic coformers. The ΔpKa value obtained is 0.7 for Aspirin and Benzoic acid, which indicates that it is favourable to form cocrystals. [1, 2, 3, 4.]

5. Supramolecular synthon: A supramolecular synthon refers to a structural motif within a supermolecule that can be formed through established or possible intermolecular forces. These units play a key role in the design of crystal structures, as they often result in repeating patterns of molecular interactions.

A synthon is an arrangement of atoms or functional groups that interact through non-covalent forces (like hydrogen bonding or van der Waals interactions) and lead to the formation of organized supramolecular structures. A supramolecular synthon involves a regular and predictable pattern of interactions, combining molecular and supramolecular components commonly found in crystal structures.

It is classified into two types:

1. Homosupramolecular Synthons involve identical functional groups that interact with each other, typically through non-covalent interactions such as hydrogen bonding.
   Ex: Two carboxylic acid groups forming hydrogen bonds.
2. Heterosupramolecular Synthons consist of different but complementary functional groups that can form stable interactions.
   Ex: Interaction between a carboxylic acid group and an amide group

Ezetimibe molecule has the C=O group and-OH groups (n=2) which can form OH---O, OH---N, O---NH backed supramolecular synthons. [5, 3, 6, 7.]

COCRYSTAL FORMATION TECHNIQUES

1. Solvent-Based Approaches

1.1. Solvent Evaporation Technique

This widely used method involves dissolving both the active pharmaceutical ingredient (API) and the coformer in a common solvent. As the solvent gradually evaporates, interactions such as hydrogen bonding between the API and coformer lead to cocrystal development. [5, 1, 2, 3, 8, 9, 10, 11, 12, 13.]

1.2. Crystallization from Solution

In this process, cocrystals form during the rapid cooling of a heated solution. The API and coformer are dissolved, and the solution is heated while stirring continuously until the volume diminishes. The resulting cocrystals are collected by filtration and dried. [5, 14.]

1.3. Slurry-Based Crystallization

Ideal for maintaining the chemical stability of components, this method involves combining the API and coformer with selected solvents to create a slurry. After allowing the solids to settle, the solvent is decanted, and the remaining solids are dried to yield cocrystals. [15.]

1.4. Antisolvent Precipitation Method

In this method, the API is evenly distributed within the coformer solution using a homogenizer. The coformer is pre-dissolved in an organic solvent and then combined with distilled water or another antisolvent. This induces the coformer to precipitate onto the drug, resulting in cocrystal formation. [16.]

1.5. Reaction-Induced Crystallization

This technique allows rapid production of cocrystals at optimal temperatures. A saturated solution of the less soluble component (typically the API) is prepared in methanol, followed by gradual addition of the more soluble coformer. The crystallization process is tracked using HPLC, while characterization is carried out using PXRD, TGA, and DSC. [14.]

2. Solid-Based Approaches

These methods are often preferred for their simplicity and reduced solvent use.

2.1 Dry Grinding

The API and coformer are mixed in a specific ratio and mechanically ground together. [4, 5, 16, 17.]

2.2 Liquid Assisted grinding

Similar to dry grinding, but involves the addition of a small amount of solvent during the grinding process. [2, 4, 6, 7, 10, 17.]

3. Ultrasound-Enhanced Crystallization from Solution/Sono-crystallization:

Used primarily for producing nanoscale cocrystals, this method involves dissolving the API and coformer in a solvent, followed by sonication. The solution becomes turbid as ultrasound is applied, and temperature is regulated using cold water to avoid particle breakage. After drying, the cocrystals are examined for purity using XRD. [18, 19.]

4. Supercritical Fluid Atomization

In this method, a supercritical fluid such as carbon dioxide is used to mix the API and coformer under high pressure. The solution is then atomized, triggering cocrystal formation through the

antisolvent effect of the supercritical fluid—this is known as the Supercritical Antisolvent (SAS) technique.

5. Spray Drying

This technique is fast, efficient, and continuous. A solution or suspension containing the API and coformer is atomized along with hot air, which rapidly removes the solvent and facilitates the formation of cocrystals. [16.]

6. Hot Melt Extrusion

This method involves applying heat and shear force to a mixture of API and coformer, promoting crystal formation through intensive mixing. It is suitable for compounds that remain stable at elevated temperatures. [16, 20.]

CHARACTERISATION OF COCRYSTALS:

In pharmaceutical development, cocrystals are particularly valuable because they allow modification of a drug's physicochemical properties—such as solubility, stability, and dissolution rate—without affecting its pharmacological action.

To confirm that a cocrystal has been successfully formed and to distinguish it from other forms such as salts, solvates, polymorphs, or physical mixtures, several analytical techniques are employed. These techniques provide comprehensive information on crystal structure, thermal behaviour, molecular interactions, and morphology.

1. Powder X-Ray Diffraction (PXRD)

PXRD is one of the primary methods used to identify cocrystals. It reveals the crystalline structure of a material by measuring how X-rays scatter off the crystal lattice. A newly formed cocrystal will produce a diffraction pattern that is different from those of the individual API and coformer, indicating a unique solid-state form.

PXRD is also useful for assessing sample purity, detecting polymorphs, and verifying reproducibility in production. The appearance of new peaks or the loss of original peaks in the pattern signifies the creation of a new crystalline phase. The characteristic peaks of telmisartan and phthalic acid got shifted; the formation of new peaks indicates the synthesis of new crystalline phase. [14] A characteristic peak was shown at 2°θ=10.00, 10.06, 10.10 and 11.24 with appearance of number of peaks, which indicate possibility of crystal lattice formation between telmisartan and coformers. [2, 3, 6.] Diffraction peaks of Canagliflozin-Thiourea cocrystals was shown at 2°θ values suggesting crystalline nature of cocrystals. [4, 18, 21.]

2. Differential Scanning Calorimetry (DSC)

DSC is a thermal analysis technique that measures energy changes in a material as it is heated or cooled. Cocrystals generally show a single, sharp melting peak that is different from the melting points of the original API and coformer.

This distinctive thermal signature confirms the formation of a new compound. DSC is also used to examine thermal stability and potential incompatibility between the components. [5] In the thermogram of cocrystal of Aspirin-Benzoic acid the respective peaks were absent, instead a sharp peak at 106.67°c has appeared showing physicochemical interaction of Aspirin and Benzoic acid. [1, 3.] The Candesartan-Benzoic acid cocrystals has sharp endothermic peak with melting point at 131.6°c, which is between melting point values of Candesartan and Benzoic acid. [8, 9.] The decrease in melting point of Cefixime-Nicotinamide to 178.96°c from 200.92°c, which is

between API and conformer, which suggests formation of interaction between carboxylic group of Cefixime and amide group of Nicotinamide. [7, 12, 22.]

3. Thermogravimetric Analysis (TGA)

TGA evaluates weight changes in a substance when exposed to increasing temperatures. It helps in assessing thermal stability and identifying any solvent or water molecules trapped in the crystal lattice.

For cocrystals, a stable weight profile up to the melting point indicates the absence of solvents or water, confirming that the sample is not a hydrate or solvate. A weight loss at lower temperatures could suggest the presence of volatile components, indicating a different solid form. [23, 24.]

4. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR provides insight into the functional groups and bonding interactions in a sample. It is especially useful for detecting hydrogen bonding, which plays a key role in cocrystal formation.

When a cocrystal forms, specific absorption bands in the IR spectrum shift due to changes in bonding environments. These shifts confirm interactions such as hydrogen bonding between the API and coformer that are not present in the individual components. [1.]

A carboxylic acid can act as a coformer, forming a neutral hydrogen bond of the type O–H···N between the acid (proton donor) and a base (proton acceptor). The IR (infrared) spectra of a neutral carboxylic acid group and a carboxylate anion show significant differences due to changes in bonding.

In a carboxylate anion ($-COO^-$), the C–O stretching vibrations appear as distinct bands in the fingerprint region, typically between 1000–1400 cm^{-1}, due to resonance and delocalization of the negative charge.

In contrast, a neutral carboxylic acid (-COOH) shows: A prominent C=O stretching absorption near 1700 cm^{-1}, and; A weaker C–O stretching band near 1200 cm^{-1}.

When a neutral O–H···N hydrogen bond is formed between the acid and a base, two broad absorption bands may appear in the IR spectrum, typically around 2450 cm^{-1} and 1950 cm^{-1}, indicating strong hydrogen bonding interactions.

Shifts in the peaks strongly suggest the presence of weak interactions and the formation of hydrogen bonds between Ezetimibe and Glycine. [3, 5.] Peak broadening was observed near wave number 3100cm^{-1} which indicates formation of intermolecular hydrogen bonding between Candesartan and Benzoic acid respective carboxylic groups. [6, 8.] Cefixime–Nicotinamide cocrystals exhibited changes in the peak intensity of O–H and C=O functional groups compared to pure Cefixime. [7, 11, 24.]

5. Solid-State Nuclear Magnetic Resonance (SS-NMR)

SS-NMR allows detailed analysis of the local atomic environment in solid materials. By observing changes in chemical shifts, it becomes possible to confirm whether a new solid-state arrangement has been formed.

Although more complex and time-consuming, SS-NMR provides deeper insight into molecular interactions within the cocrystal and is highly reliable when other techniques are inconclusive.

6. Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) is employed to examine the surface morphology and determine the particle size of a sample. It helps in distinguishing cocrystals from physical mixtures by revealing differences in crystal shape and surface structure.

Cocrystals often appear more uniform and structured compared to physical mixtures, where API and coformer particles retain their original, separate identities. The morphology of Candesartan-benzoic acid cocrystals has appeared as needle-shaped. [8] The morphology of the Rosuvastatin–Asparagine and Rosuvastatin–Glutamine cocrystals appeared as tightly packed clusters, indicating structural changes likely due to intermolecular hydrogen bonding between the API and the conformer. [6, 9, 13, 22, 25.]

7. Single-Crystal X-Ray Diffraction (SCXRD)

SCXRD is the definitive method for confirming cocrystal formation. It provides precise atomic-level information about the crystal structure, including the arrangement of molecules and the nature of intermolecular interactions.

This technique conclusively verifies whether a new cocrystalline structure has formed. However, growing suitable single crystals can be challenging, which limits the routine use of SCXRD despite its accuracy.

8. Hot Stage Microscopy (HSM)

HSM involves observing a sample under a microscope while heating it in a controlled manner. This allows researchers to see how the material changes with temperature in real-time.

It's a supportive tool used alongside DSC to visualize melting points and phase changes, helping identify whether the observed thermal events are due to true cocrystal transitions or physical mixtures. Ezetimibe-Glycine cocrystals complete melting was observed at 174°c which is between melting point of API and Coformer, which concludes the interaction between API and Coformer. [5.]

9. Raman Spectroscopy

Raman spectroscopy is a vibrational spectroscopic method that serves as a complementary technique to FTIR, providing additional insights into molecular vibrations and structural information. It is particularly useful for identifying molecular interactions and chemical bonding in non-polar environments.

When a cocrystal forms, specific vibrational modes shift, indicating new molecular interactions. These spectral changes support evidence from other techniques and help confirm the formation of a cocrystal. The O–H stretching band of the carboxylic group in Candesartan exhibited a shift to a lower wavenumber by 3 cm^{-1}, indicating its involvement in hydrogen bonding [6, 8, 17.]

10. Solubility and Dissolution Studies

Functional characterization is as important as structural analysis, particularly in pharmaceutical applications. These studies assess how the cocrystal performs in terms of solubility and dissolution compared to the original drug.

Improved solubility or a faster dissolution rate suggests that the cocrystal could enhance the drug's bioavailability, making it more effective for therapeutic use. This testing is crucial, especially for poorly soluble drugs where cocrystals are developed to overcome formulation challenges.

Dissolution study of Telmisartan-citric acid cocrystals has shown good dissolution rate when compared to pure API, nearly 1.6-fold increase in

dissolution rate was observed and Solubility of cocrystals was also comparatively high as compared to pure API. [3] The dissolution problem of Candesartan has been overcome as the Candesartan-Benzoic acid cocrystals has shown 85.22%, where as pure API only shows 18.42%. [8] The Solubility issue was resolved when Rosuvastatin-Asparagine cocrystal showed 2.17-fold increase in solubility, and Rosuvastatin-Glutamine cocrystal showed 1.64-fold increase in solubility. [6, 9, 12, 13.]

The characterization of pharmaceutical cocrystals involves a wide range of analytical methods that explore structural, thermal, chemical, and performance-related properties. Techniques such as PXRD and DSC are essential for initial identification, while SCXRD offers definitive structural validation. Additional methods like TGA, FTIR, SS-NMR, SEM, and Raman spectroscopy enrich the analysis and help build a complete picture of the cocrystal's nature.

Evaluating solubility and dissolution behaviour ensures that cocrystals not only exist as new solid forms but also offer practical advantages in drug delivery. Together, these methods ensure a comprehensive understanding of cocrystal formation, stability, and potential benefits, making them a powerful tool in modern pharmaceutical development.

APPLICATIONS OF COCRYSTALLIZATION

Cocrystallization, as a crystal engineering strategy, enhances the physicochemical characteristics of active pharmaceutical ingredients (APIs) without altering their chemical structure. This technique is particularly beneficial in the pharmaceutical field, where it is used to improve the solubility and dissolution rate of drugs with poor water solubility, thereby increasing their bioavailability. Additionally, cocrystals can enhance other essential properties such as tabletability, permeability, and overall stability, making them a valuable approach in modern drug formulation and development.

1. Stability:

Accelerated stability studies of cocrystals GLZ–3,5-dinitrosalicylic acid (DNS), GLZ-2,6-pyridine dicarboxylic acid (PDA), and GLZ– 2,6-pyridine dicarboxylic acid (LPN) were performed at 40 ± 5 °C/75 ± 5% RH for 3 months (90 days). The results obtained from the PXRD studies showed no significant changes in crystallinity after 1 month (30 days), 2 months (60 days), and 3 months (90 days), respectively. [6, 11, 25.]

2. Solubility:

Low Solubility Drugs such as BCS class-II drugs, solubility can be enhanced by cocrystal formation. Example: Ezetimibe a BCS class-II drug having low solubility of 120.20±2.3 has increased to 306.44±3.1 after forming cocrystals with glycine. [5] Solubility problem of Telmisartan was resolved when cocrystallised with Phthalic acid, Hydrochlorothiazide and Citric acid individually. [2, 3, 14.] Candesartan exhibits a solubility of 2.032 ± 0.050 mg/mL, while its cocrystal form shows a significantly higher solubility of 3.606 ± 0.074 mg/mL. This suggests that there has been an enhancement of 1.78-fold in the solubility of candesartan after co-crystallization. [8] Canagliflozin-Thiourea [18], all these cocrystals when analysed showed increased solubility with respect to the pure API. [6] Hydrochlorothiazide-Nicotinamide cocrystals has shown 2-fold increase in solubility. [4, 13, 20, 26.]

3. Permeability:

For Cocrystals permeability is a key factor in bioavailability, especially for orally administered drugs. While cocrystals are primarily known for improving solubility and dissolution, they can also influence permeability — directly or indirectly. Hydrochlorothiazide-Nicotinamide cocrystals cocrystals has shown increased permeability properties when compared to the pure Hydrochlorothiazide. [20] The permeation rate of Cefixime–Nicotinamide cocrystals was found to be 1.99 times higher than that of pure Cefixime. [7, 21].

4. Flowability:

Cocrystals can improve the flow properties of an active pharmaceutical ingredient (API), particularly when the API in its pure form is poorly flowable. Improved flow properties were observed in Telmisartan-Hydrochlorothiazide cocrystals when compared to the Pure Telmisartan. [2, 26].

5. Melting point:

The melting point of a cocrystal is a key physical property that can help distinguish it from its individual components (the pure compounds). The melting point of a cocrystal typically falls between the melting points of its two individual components—the API and the coformer. However, it may also be higher or lower than both components depending on the nature of intermolecular interactions (e.g., hydrogen bonding, π–π stacking). Melting point of Canagliflozin-Thiourea cocrystal was found to be 100°c which is between melting points of API and conformer. [16, 18].

6. Biological Activity:

By improving the drug's ability to dissolve and be absorbed, cocrystals can increase its systemic exposure. This approach is particularly beneficial for BCS Class II drugs, which have low solubility but high permeability. The biochemical half maximal inhibitory concentration (IC50) of the 5-fluorouracil-Nicotinamide cocrystal was calculated for 72h and it suggests that the IC50 of cocrystals is less than pure 5-fluorouracil, therefore cocrystal is more effective at inhibiting tumour cell proliferation in cell culture. [10, 12, 23].

CONCLUSION:

Co-crystallisation proves to be a potential method to improve properties of various drugs of BCS classes, especially BCS class-II and IV which have Solubility and Permeability issues. Pharmaceutical cocrystals offer a promising strategy to enhance the properties of active pharmaceutical ingredients (APIs) without changing their therapeutic action. Through the formation of non-covalent interactions like hydrogen bonds and π–π interactions, cocrystals can significantly improve solubility, stability, bioavailability, and ease of manufacturing. The effectiveness of this approach relies on careful selection of coformers and appropriate synthesis techniques. Comprehensive characterization ensures accurate identification and performance assessment. In summary, cocrystals provide a valuable solution for overcoming formulation limitations, contributing to more effective drug delivery systems and improving overall treatment outcomes in modern pharmaceutical development.

CONFLICT OF INTEREST: The authors have no conflicts of interest.

REFERENCES

1. Dutt. B, Choudhary. M & Budhwar. V: Preparation, characterization and evaluation of aspirin: benzoic acid cocrystals with enhanced pharmaceutical properties. Future Journal of Pharmaceutical Sciences 2020;

6:32. https://doi.org/10.1186/s43094-020-00052-y

2. Kulkarni. A, Shete. S, Hol. V, and Bachhav. R: "Novel Pharmaceutical Cocrystal of Telmisartan and Hydrochlorothiazide: Co-crystals". Asian Journal of Pharmaceutical and Clinical Research, Mar. 2020; 13(3): 104-12. doi:10.22159/ajpcr.2020.v13i3.36541. https://www.researchgate.net/publication/339903133_NOVEL_PHARMACEUTICAL_COCRYSTAL_OF_TELMISARTAN_AND_HYDROCHLOROTHIAZIDE
3. Arora P, Kaur A, Haneef J and Chadha R: Solubility improvement of Telmisartan by cocrystallization with citric acid. Int J Pharm Sci Res 2017; 8(9): 3768-75. doi: 10.13040/IJPSR.0975-8232.8(9).3768-75. https://ijpsr.com/bft-article/solubility-improvement-of-telmisartan-by-cocrystallization-with-citric-acid/
4. Kumar. S, Gupta. A, Mishra C. K and Singh. S: Synthesis, Characterization and Performance Evaluation of Aceclofenac-Urea Cocrystals. Indian Journal of Pharmaceutical Sciences 2020; 82(5): 881-890. https://www.ijpsonline.com/articles/synthesis-characterization-and-performance-evaluation-of-aceclofenacurea-cocrystals.pdf
5. Anand. R, Nanda. A: Formulation and Evaluation of Cocrystals of a BCS class II Drug using Glycine as conformer. International Journal of Applied Pharmaceutics 2022; 14(6): 68-76. https://www.researchgate.net/publication/365612221_FORMULATION_AND_EVALUATION_OF_COCRYSTALS_OF_A_BCS_CLASS_II_DRUG_USING_GLYCINE_AS_COFORMER
6. Eesam. S, Bhandaru J.S., Akkinepally R.R. et al: Cocrystallization of gliclazide with improved physicochemical properties. Futur J Pharm Sci 2021; 7 (124). https://doi.org/10.1186/s43094-021-00261-z
7. Abdullah, A., Mutmainnah, M., & Wikantyasning, E. R: Cocrystals of Cefixime with Nicotinamide: Improved Solubility, Dissolution, and Permeability. Indonesian Journal of Pharmacy 2022; 33(3), 394-400. https://doi.org/10.22146/ijp.2530
8. Fatima, D. Z: Tailoring the Dissolution Rate of Candesartan through Cocrystal Formation. Asian Journal of Pharmaceutics 2018. 12(03), 196-203. https://doi.org/10.22377/ajp.v12i03.2573
9. Vemuri, V.D., Lankalapalli, S: Rosuvastatin cocrystals: an attempt to modulate physicochemical parameters. Futur J Pharm Sci 2021; 7(64). https://doi.org/10.1186/s43094-021-00213
10. Zhuyan Zhang, Nan Yu, Chang Xue, Shan Gao, Zhaopeng Deng, Min Li, Cong Liu, John Castellot and Siying Han: Potential Anti-Tumor Drug: Co-Crystal 5-Fluorouracil-nicotinamide. ACS Omega 2020, 5(26), 15777-15782. DOI:10.1021/acsomega.9b03574 https://pubs.acs.org/doi/10.1021/acsomega.9b03574
11. Anusha. B, Sunitha M. R: Solubility Enhancement of Sertraline by Solvent Evaporation Co-Crystal Technique. International Journal of Pharmacy and Biological Sciences 2019; 9(1): 988-1002; DOI: https://doi.org/10.21276/ijpbs.2019.9.1.127
12. Na Wu, Yan Zhang, Jian Ren, Aiguo Zeng, Juntian Liu: Preparation of quercetin–nicotinamide cocrystals and their evaluation under in vivo and in vitro conditions. RSC Advances Journal, 37, 2020; https://pubs.rsc.org/en/content/articlelanding/2020/ra/d0ra03324c

13. H. K., S., H. V., J., Radhakrishna, M., B. H., J. G., Paul, K., Shankar, S. J., Ahmed, M. G., & A., S: Enhancement of Solubility and Dissolution Rate of Acetylsalicylic Acid via Co-Crystallization Technique: A Novel Asa-Valine Cocrystal. International Journal of Applied Pharmaceutics 2021; 13(1), 199–205. https://doi.org/10.22159/ijap.2021v13i1.40054
14. Kundu S, Kumari N, Soni SR, Ranjan S, Kumar R, Sharon A, Ghosh A: Enhanced Solubility of Telmisartan Phthalic Acid Cocrystals within the pH Range of a Systemic Absorption Site. ACS Omega. 2018 Nov 13;3(11):15380-15388. doi: 10.1021/acsomega.8b02144. PMID: 31458196; PMCID: PMC6644309. https://pmc.ncbi.nlm.nih.gov/articles/PMC6644309/#:~:text=The%20characteristic%20peaks%20of%20telmisartan,same%20cocrystal%20form%20or%20composition
15. Junguang Yu, Rodger F. Henry, Geoff G.Z. Zhang: Cocrystal screening in minutes by solution-mediated phase transformation (SMPT): Preparation and characterization of ketoconazole cocrystals with nine aliphatic dicarboxylic acids. Journal of Pharmaceutical Sciences Jan 2025; 114(1) 592-598. https://www.sciencedirect.com/science/article/pii/S0022354924004969
16. Bose P, Chandra S, Das A, Roy T, Paul S and Mukherjee L: Enhancement of solubility of an oral hypoglycaemic drug, glimeperide by the technique cocrystallisation. Int J Pharm Sci & Res 2021; 12(2): 1092-08. doi: 10.13040/IJPSR.0975-8232. file:///C:/Users/Dell/Downloads/47-Vol.-12-Issue-2-Feb-2021-IJPSR-RA-14130.pdf
17. MD Sadeque Hossain Mithu, Steven A. Ross, Andrew P. Hurt, Dennis Douroumis: Effect of mechanochemical grinding conditions on the formation of pharmaceutical cocrystals and co-amorphous solid forms of ketoconazole – Dicarboxylic acid. Journal of Drug Delivery Science and Technology 2021; 63,102508. https://doi.org/10.1016/j.jddst.2021.102508.
18. Burkhande, N. S., Wankhade, V. P., Atram, S. C., Bobade, N. N., & Pande, S. D: Development of Co-Crystallization Technique to Improve Solubility of Anti-Diabetic Drug. Asian Journal of Pharmaceutical Research and Development 2023; 11(4): 30–35. https://doi.org/10.22270/ajprd.v11i4.1282
19. Salem A, Takácsi-Nagy A, Nagy S, Hagymási A, Gősi F, Vörös-Horváth B, Balić T, Pál S, Széchenyi A: Synthesis and Characterization of Nano-Sized 4-Aminosalicylic Acid-Sulfamethazine Cocrystals. Pharmaceutics 2021 Feb 19;13(2):277. doi: 10.3390/pharmaceutics13020277. PMID: 33669489; PMCID: PMC7923100. https://pmc.ncbi.nlm.nih.gov/articles/PMC7923100/
20. Narala S, Nyavanandi D, Alzahrani A, Bandari S, Zhang F, Repka MA: Creation of Hydrochlorothiazide Pharmaceutical Cocrystals Via Hot-Melt Extrusion for Enhanced Solubility and Permeability. AAPS PharmSciTech. Jan 2022; 18;23(1):56. doi: 10.1208/s12249-021-02202-8. PMID: 35043282.https://pubmed.ncbi.nlm.nih.gov/35043282/
21. Meng Y, Tan F, Yao J, Cui Y, Feng Y, Li Z, Wang Y, Yang Y, Gong W, Yang M, Kong X, Gao C: Preparation, characterization, and pharmacokinetics of rivaroxaban cocrystals with enhanced in vitro and in vivo properties in beagle dogs. International Journal of Pharmaceutics 2022 May 21; 4: 100119. doi: 10.1016/j.ijpx.2022.100119. PMID: 35663355; PMCID: PMC9160491. https://pmc.ncbi.nlm.nih.gov/articles/PMC9160491/

22. K. Blessi Priyanka, B. Bhagya, Shayeda, Characterization And Solubility Studies Of Pharmaceutical Cocrystals of Paliperidone, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 7, 209-215. https://doi.org/10.5281/zenodo.12623907 https://www.ijpsjournal.com/assetsbackoffice/uploads/article/Characterization+And+Solubility+Studies+Of+Pharmaceutical+Cocrystals+Of+Paliperidone.pdf
23. Gomes SN, Biscaia IFB, Lopes DS, Mengarda M, Murakami FS, Oliveira PR, Bernardi LS: Cocrystals Enhance Biopharmaceutical and Antimicrobial Properties of Norfloxacin. Pharmaceutics. 2023; 15(9):2211. https://doi.org/10.3390/pharmaceutics15092211
24. Ma P, Toussaint B, Roberti EA, Scornet N, Santos Silva A, Castillo Henríquez L, Cadasse M, Négrier P, Massip S, Dufat H, Hammad K, Baraldi C, Gamberini MC, Richard C, Veesler S, Espeau P, Lee T, Corvis Y: New Lidocaine-Based Pharmaceutical Cocrystals: Preparation, Characterization, and Influence of the Racemic vs. Enantiopure Coformer on the Physico-Chemical Properties. Pharmaceutics. 2023 Mar 29;15(4):1102. doi: 10.3390/pharmaceutics15041102. PMID: 37111588; PMCID: PMC10142540. https://pmc.ncbi.nlm.nih.gov/articles/PMC10142540/
25. Li Z, Matzger AJ: Influence of Coformer Stoichiometric Ratio on Pharmaceutical Cocrystal Dissolution: Three Cocrystals of Carbamazepine/4-Aminobenzoic Acid. Mol Pharm 2016 Mar; 7;13(3):990-5. doi: 10.1021/acs.molpharmaceut.5b00843. Epub 2016 Feb 3. PMID: 26837376; PMCID: PMC4975166. https://pmc.ncbi.nlm.nih.gov/articles/PMC4975166/
26. Bhakti Pawar, Dr. Afaque Raza Mehoboob Ansari, Modulating the Solubility of Mesalamine by Means of Cocrystals, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 6, 1909-1923.https://doi.org/10.5281/zenodo.15629710

HOW TO CITE: R. Satya Deepthi, M. Sunitha Reddy, K. Anie Vijetha, A Review on Pharmaceutical Cocrystals – Preparation, Characteristics and Applications, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 8, 1695-1706. https://doi.org/10.5281/zenodo.16882709