

**Review Article**

**ADVANCES IN COCRYSTALS OF ANTICANCER AGENTS: FORMULATION STRATEGIES AND THERAPEUTIC IMPLICATIONS**

**APARNA SINGH, VISHAKHA JAISWAL\*, SHRADHA BISHT**

Amity Institute of Pharmacy, Lucknow, Amity University Uttar Pradesh, Sector 125, Noida-201313, India

\*Corresponding author: Vishakha Jaiswal; \*Email: vishakhajaiswal216@gmail.com

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**ABSTRACT**

Cancer remains one of the most pressing health concerns worldwide, driving continuous efforts in pharmaceutical research to develop more effective treatments. In the ever-evolving landscape of cancer therapy, cocrystals stand as promising contenders, offering enhanced solubility, stability, and bioavailability to traditional anticancer agents. Co-crystallization, a strategy emerging at the nexus of pharmaceutical and crystal engineering. From the fundamental principles of cocrystal engineering to advanced spectroscopic and crystallographic methodologies, each aspect is meticulously dissected to unveil the transformative potential of cocrystals in oncology. The review elucidates the transformative potential of cocrystals in oncology, highlighting their capacity to revolutionize drug delivery and efficacy. Recent advancements in the field are comprehensively examined, showcasing the promising role of anticancer cocrystals in paving the way for novel therapeutic strategies and improved patient outcomes. Cocrystals represent a promising avenue in cancer therapy, offering significant enhancements to traditional anticancer agents. Through a comprehensive exploration of recent advancements, this article navigates the complex terrain of anticancer cocrystals, drug-drug cocrystals, paving the way for novel therapeutic strategies and improved patient outcomes.

**Keywords:** Cocrystal, Cancer, Drug-drug co-crystal, Co-former, Green synthesis, Synthon approach

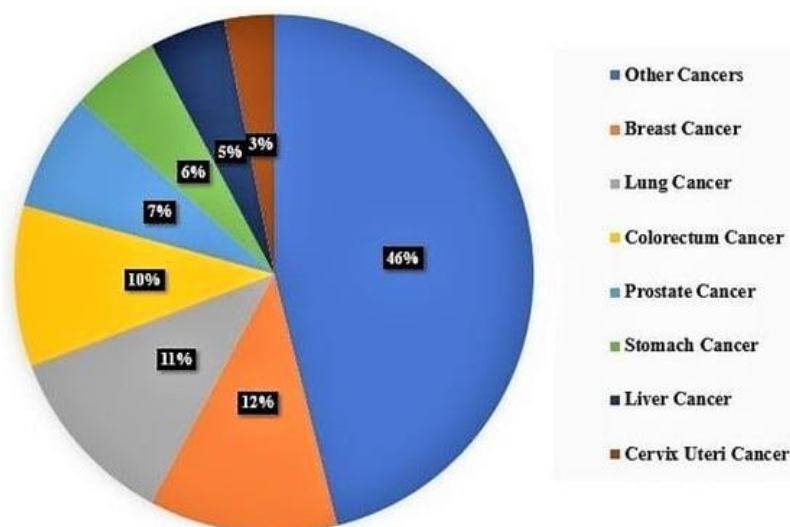
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**INTRODUCTION**

Cancer stands as a prominent catalyst for the escalating global mortality rates and remains a paramount public health challenge worldwide [1]. With one in every six deaths attributed to cancer, its impact on mortality rates cannot be overstated [2]. The Global Cancer Observatory (GCO) projects a staggering 10 million deaths related to cancer, alongside an estimated 19 million new cases in the year 2020 alone [3]. Despite these stark statistics underscoring the ongoing battle against cancer, it is disheartening to note that the "war on cancer" remains far from

won, as evidenced by projections indicating a staggering toll of sixteen million lives lost and three billion new cases globally over the next decade [4].

The spectrum of cancers is vast and encompasses a myriad of types, including but not limited to kidney cancer, pancreatic cancer, uterine cancer, bladder cancer, skin cancer, prostate cancer, non-Hodgkin lymphoma, leukemia, endometrial cancer, colorectal cancer, lung cancer, melanoma, breast cancer, liver cancer, and thyroid cancer [5]. Refer to fig. 1 for an illustration depicting data and facts concerning various cancer types.



**Fig. 1: Statistical data and factual information regarding various types of cancer [6]**

Over the past decade, healthcare professionals have grappled with heightened cancer prevalence. Progress in science and technology

has been instrumental in addressing gaps in the field, particularly in advancing medicinal treatments. Historically, cancer treatment

primarily relied on parenteral administration, but in recent decades, oral administration has gained traction due to its convenience and dosing frequency [7].

Oral drug delivery stands out as a popular and well-established method, offering benefits such as enhanced patient comfort, acceptability, and safety. The customisable nature of formulations based on the physicochemical properties of medicinal ingredients adds to their appeal within the scientific community. However, the efficacy of orally administered cancer chemotherapeutic drugs is impeded by challenges like the significant first-pass effect, higher efflux ratio, lower water solubility, impermeability, and reduced bioavailability [8].

Anticancer drugs constitute about 75% of newly developed chemical compounds, which are predominantly known for their poor water solubility [9]. This limited solubility poses a significant challenge to their development and practical application. According to the Biopharmaceutics Classification System (BCS), drugs are categorized as weakly water-soluble if their highest dosage strength fails to dissolve in 250 ml or less of water across a pH range of 1 to 7.4 [10]. Unfortunately, numerous anticancer drugs such as dasatinib [11], curcumin [12], docetaxel [13], and paclitaxel [14] fall into BCS classes II and IV due to their low solubility. Despite this challenge, many of these drugs possess potential antineoplastic efficacy. Their high lattice energies render them less soluble than micrograms per millilitre, hindering their dissolution and interaction with water molecules [15].

Since oral administration remains the most feasible route, over 80% of commercial drugs are formulated in solid doses like tablets and capsules [16]. In solid-state formulations, the physicochemical

properties of drugs can be modified using methods such as co-crystals, polymorphs, salts, amorphous forms, and hydrates [17]. However, due to the risk of polymorphic transformation, which can impact the final product, polymorphs are generally not recommended [18]. Consequently, new strategies must be devised to modify or improve the physicochemical properties of these drugs [19].

Co-crystals, as defined by the Food and Drug Administration (FDA), are crystalline solids comprising two or more distinct molecules. In pharmaceutical contexts, Active Pharmaceutical Ingredients (APIs) often engage in crystal lattice formation through non-ionic interactions with co-formers or co-crystal formers (Food and Drug Administration, 2018). Over recent years, co-crystals have shown significant advancement in drug development, particularly in modifying the physicochemical and pharmacokinetic attributes of APIs. These modifications include enhancements in solubility, dissolution rate, particle size, melting point, bioavailability, morphology, biochemical stability, physical form, and permeability [20]. Additionally, numerous research studies have explored the application of co-crystals in drug delivery [21].

Moreover, Yuliandra *et al.*'s investigation into the *in vivo* efficacy of the ibuprofen-nicotinamide (IBU-NIC) co-crystal in male Swiss-Webster rats demonstrated that co-crystal production could enhance the analgesic effectiveness of the compound. Results indicated a doubling in pain inhibition with the IBU-NIC co-crystal compared to ibuprofen alone or its physical combination [22, 23]. Moreover, as depicted in fig. 2, active pharmaceutical ingredients (APIs) can create multi-component crystals in a singular form.

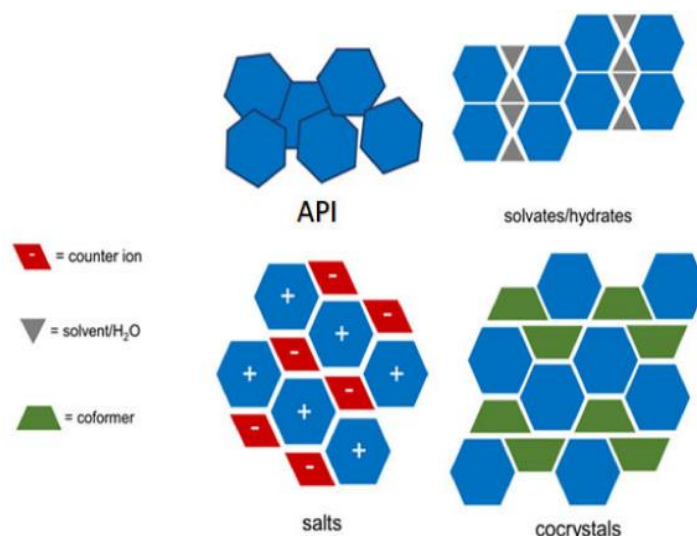


Fig. 2: Various pharmacological forms for API that are solid and multicomponent [24]

Lawton and Lopez did not introduce the term "co-crystal" until 1963. Co-crystals are characterized as multicomponent crystals consisting of co-formers and APIs, featuring non-covalent intermolecular bonding interactions such as van der Waals forces,  $\pi$ - $\pi$  stacking, hydrogen bonds, and halogen bonds. Supramolecular synthons, alternatively known as homo- or hetero-synthons, emerge when functional groups within a crystal repeatedly interact with one another through proton donors and acceptors. These synthons may comprise identical functional groups or diverse ones [19].

The data was collected from Elsevier-Science Springer Link, PubMed, National Library of Medicine (NLM), Semantic Scholar, and Google Scholar to conduct a literature search mostly from 2022 to 2024. The reference articles selected for this work are those that describe the current trends in co-crystallization techniques, characterization spectral techniques used, latest drug cocrystals for various cancer for management purpose, patient care and improving quality of life.

#### Co-former screening and selection techniques

Selecting the perfect co-former is imperative for accessing cocrystals with desired qualities. Simultaneously, the crystal engineering of APIs poses a formidable task. The process of cocrystal formation faces its greatest challenge during the selection of suitable co-formers, as the array of potential candidates often exceeds hundreds and multiple validation methods are commonly employed [25]. Supramolecular chemistry underpins the synthesis of cocrystals, with hydrogen bonding being the predominant intermolecular bonding motif among most APIs and co-formers. Thus, the choice of the optimal co-former remains pivotal for achieving cocrystals with the desired attributes [26].

#### Theoretical approaches

Various theories, including "Hydrogen bonding propensity," "Cambridge Structure Database," "supramolecular synthon," "acid dissociation constant (pKa) values," and "Hansen solubility

parameters," were utilized in elucidating the genesis of cocrystals [27]. Etter's pragmatic directives on hydrogen bonding for constructing such solids could provide the fundamental framework for understanding hydrogen bonding synthons in cocrystals. Etter's investigation into the controllability of hydrogen bonding within established crystal structures aimed to regulate the hydrogen-bond assembly of chemical compounds generating crystals. Consequently, he proposed a series of pragmatic principles governing hydrogen bonding [27, 28]. The subsequent elucidation outlines Etter's trio of hydrogen-bonding guidelines:

- All reliable proton donors and acceptors participate in hydrogen bonding.
- Six-membered-ring intramolecular hydrogen bonds form, unlike intermolecular hydrogen bonds.
- Following the establishment of intramolecular hydrogen bonds, the remaining proton donors and acceptors above create intermolecular hydrogen bonds with each other.

### Supra molecular synthon approach

Cocrystals emerge from noncovalent interactions between a drug and co-formers, such as hydrogen bonds, van der Waals forces, and pi-pi stacking. Supramolecular synthons, defined as structural units within super molecules, can be formed through known or anticipated synthetic methods involving intermolecular interactions, as proposed by Desiraju's [29] model of the supramolecular synthon

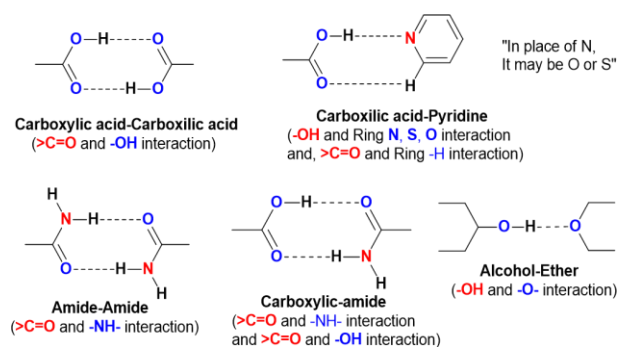


Fig. 3: Hydrogen bonding between suitable functional groups of drugs and co-former according to supramolecular synthon approach [29]

### Preparation methods of co-crystals

The two most common methods of cocrystal production are solution crystallization and solid-state crystallization. The methods used to generate cocrystals can be broadly divided into three categories: solvent-based, supercritical fluid approaches, and green synthesis methods (also known as non-solvent-based methods) [32].

### Green synthesis techniques or non-solvent techniques

Non-solvent techniques offer environmental advantages as they require minimal or no solvent for the creation of cocrystals. These methods, namely Liquid-Assisted grinding (LAG), extrusion, simple/neat grinding, and hot-melt extrusion, fall into four distinct categories [33]. The neat grinding approach involves blending two or more co-formers according to a predetermined stoichiometry and then mechanically or physically grinding them for a set duration. Except for the minimal use of organic solvent during grinding, the LAG method closely resembles neat grinding [34]. In the extrusion process, co-formers and the Active Pharmaceutical Ingredient (API) are combined below the raw material's melting point using either a single screw or twin screws. Conversely, hot-melt extrusion is a specialized technique that simultaneously melts and mixes co-formers using a hot screw extruder [35].

### Solvent-based techniques

Various solution-based techniques, including evaporative, spray drying, solvent evaporation, slurry, and reactive co-crystallization,

are recognized for their ability to produce cocrystals. Solvent serves as a medium in the co-crystallization process, involving undersaturated solutions of both the co-former and the API [36].

- Identifying functional groups within the active pharmaceutical ingredient (API) and co-former molecules.
- evaluating intramolecular interactions within the isolated molecules of the desired compounds.
- recognizing potential functional groups that could hinder intramolecular interactions in pure compounds.
- evaluating the probability of intermolecular interactions between different molecules.
- choosing co-formers through analysing both intramolecular and intermolecular interactions.

### Cambridge Structural Database (CSD)

The CSD serves as a crucial tool in elucidating intermolecular hydrogen bonding within crystals [30], playing a pivotal role in advancing various fields such as chemistry, materials science, life sciences, and pharmaceutical research. With its robust design and efficiency, the CSD continually incorporates approximately 40,000 new structures annually [31]. Furthermore, it can be leveraged to anticipate stable hydrogen bond motifs, thereby preserving the most robust patterns across a range of core structures. Additionally, the CSD offers the advantage of facilitating the development of cocrystals through techniques like the hydrogen bonding potential (HBP).

Formation of ketoprofen-malic acid cocrystal by solvent evaporation method. This method typically yields single-crystal cocrystals suitable for diffraction studies and crystal structure characterization. Similarly, assisted evaporation co-crystallization, conducted under controlled conditions, resembles the solvent evaporation method but occurs at higher temperatures and/or lower pressure [37].

Although spray drying is commonly employed for producing amorphous solid dispersions (ASDs), recent research indicates its potential for cocrystal synthesis. This method offers advantages due to its rapid, continuous, and precise control over the process. In spray drying, a sprayer disperses an unsaturated liquid containing both drugs and co-formers with nitrogen, facilitating rapid solvent removal and solid particle formation [38].

The slurry conversion technique, often known as isothermal slurry conversion, involves introducing solid co-formers to a solvent (or a blend of solvents) at a predetermined stoichiometric ratio to achieve equilibration. Unlike evaporative co-crystallization, this method doesn't necessitate a clear starting solution.

In reactive co-crystallization, co-formers and APIs are separately mixed before being introduced to one of the clear solutions, leading to spontaneous co-crystallization. Nanocrystal formulations can be

prepared using the ultrasound-assisted solution technique, where suitable co-formers and APIs are dissolved in a solvent. The solution undergoes sonication at a controlled temperature to prevent fragmentation and degradation, followed by overnight incubation for solvent evaporation and cocrystal formation [39].

### Supercritical fluid approach

To produce a single crystal from a complex system of multiple components, the supercritical fluid method involves heating a mixture of Active Pharmaceutical Ingredient (API) and co-former to a temperature near the melting point of one component, typically the co-former. Unlike traditional organic solvents, supercritical fluid facilitates rapid kinetics and simplifies solvent removal from the final products, reducing costs and equipment requirements for subsequent steps in cocrystal production. This technique relies on suspending both API and co-former in a supercritical CO<sub>2</sub> slurry for co-crystallization. By adjusting CO<sub>2</sub> thermodynamics to maintain its density and solvent power, control over co-crystallization between components is achieved.

The use of this method has demonstrated accelerated co-crystallization rates, resulting in complete co-crystallization and the formation of pure cocrystals due to efficient mass transfer facilitated by convection in the CO<sub>2</sub> slurry. In the Rapid Expansion of Supercritical Solvents (RESS) method, supercritical CO<sub>2</sub> saturated with API and co-former is depressurized through a nozzle into an atmospheric drying chamber. However, many pharmaceutical compounds do not exhibit the required solubility in supercritical CO<sub>2</sub> for this approach.

In the Supercritical Antisolvent Co-crystallization (SAC) procedure, supercritical CO<sub>2</sub> serves as an antisolvent. This method precipitates both molecules together as a single unit and requires less soluble API and co-former compared to RESS. Upon the introduction of components into the vessel, CO<sub>2</sub> dissolves in the solvent, expanding the volume while reducing solvent solubility and precipitating the solvent.

In the batch gas antisolvent (BGAS) method, a solution containing both API and co-former is saturated in a vessel with carbon dioxide under increased pressure until co-crystallization is achieved. Alternatively, the semi-continuous supercritical antisolvent (SSAS) technique utilizes a sprayer to inject an API-co-former solution into a vessel containing supercritical CO<sub>2</sub> under high pressure [40].

### Characterization of cocrystals

Microscopic, spectroscopic, and thermal techniques are commonly employed in the analysis of cocrystals. Various physicochemical factors such as crystallinity, melting temperature, stability, dissolution, and solubility are assessed similarly to any other solid form to ascertain the suitability of a substance for industrial dosage formulation. The melting point, a crucial physical characteristic determined by the temperature at which the solid and liquid phases reach equilibrium with zero free energy of transition, is fundamental. Differential scanning calorimetry (DSC) efficiently provides melting point and thermal data like melting enthalpy. Additionally, Differential Thermal Analysis (DTA) and Thermogravimetry (TG) are employed to ascertain factors such as

polymorphisms, glass transitions, hydration, decomposition, and stability.

Powder X-ray diffraction and single-crystal X-ray diffraction offer structural information, crystallinity level, and crystal size. Single-crystal X-ray diffraction (SCXRD) is considered the gold standard for comprehensive 3D structural, compositional, packing, and hydrogen bond information. Spectrophotometric methods like Infrared Radiation (IR), Raman, and nuclear magnetic resonance (NMR) offer insights into noncovalent interactions, such as hydrogen bonds, and detect shifts in intermolecular interactions across various crystal structures. Scanning electron microscopy (SEM) and optical microscopy are utilized for surface topography examination, particle size analysis, and optical property assessment.

Hot-stage microscopy (HSM) integrates microscopy and thermal analysis to provide solid-state characterization, especially for temperature assessment. Stability in both solid and liquid states is crucial for orally administered dosage forms. Thermal and relative humidity stress (RHS) are used to assess the potential for solid-state modifications. High-performance liquid chromatography (HPLC) is often combined with thermal techniques and powder X-ray diffraction (PXRD) for degradation testing.

Distinguishing between salt and cocrystal can be challenging. Solid-state NMR and/or IR spectra can aid in estimating proton transfer, though interpretation in a specific system may be difficult. SCXRD remains the most reliable method for identifying salt or crystals, while others are indirect and prone to error [41].

### Application of drug cocrystals in the realm of cancer treatment

Teva Pharmaceuticals has recently combined fumaric acid with the anticancer medication ibrutinib, commonly prescribed for chronic lymphocytic leukaemia, to create a cocrystal. This innovative blend, demonstrated to be more stable while maintaining comparable solubility to the original medication, presents ample opportunity for further cocrystal development. Researchers have successfully improved the physicochemical properties of numerous anticancer medications through the creation of various cocrystals. These cocrystals often incorporate carboxylic acids, polyphenols, carboxyl amides, and amides as co-formers due to their similar pKa values. Some anticancer medications, such as paclitaxel, exhibit zwitterionic properties. The majority of these medications are either mildly basic or weakly acidic [19].

The pKa rule of 3 suggests that cocrystal formation is facilitated when the pKa values of the drug and co-former fall within a range of 0 to 3. Using the  $\Delta pK_a$  rule, da Silva and colleagues synthesized cocrystals of 5-fluorocytosine with various co-formers, including terephthalic acid, benzoic acid, adipic acid, succinic acid, and malic acid [42].

In another study, Chenxin *et al.* investigated two distinct co-formers for palbociclib, utilizing orcinol and resorcinol. Palbociclib-resorcinol cocrystals exhibited enhanced powder dissolution compared to pure palbociclib. However, a notable drawback was observed: while these cocrystals improved the drug's solubility, they also increased its bioavailability [43].

**Table 1: A list of anti-cancer medication cocrystals that have been described, along with cocrystal synthesis methods and enhanced properties from pure API**

Anti-cancer drugs	Co-formers	Preparation techniques	Enhanced parameters from pure drug	Reference
5-Fluorouracil	Ferulic acid	Solvent assisted co-grinding	Improved solubility and permeability	[44]
5-Fluorouracil	Proline	Solvent evaporation technique and Liquid assisted grinding	Improved solubility, permeability	[45]
4,40-ethylene bis pyridine	Flavonoids	Solvent Evaporation method	Improved dissolution behaviour and anti-tumor activity	[46]
5-Fluorouracil	Succinic acid, Malic acid	Neat grinding and slow solvent evaporation	Improved anticancer activity	[47]
6-Mercaptopurine monohydrate	Cinnamic acid, and Benzoic acid	Slurry reactive crystallization	Improved solubility and stability	[48]
Axitinib	2,4-Dihydroxybenzoic acid and Hydroxybenzoic acid	Solvent evaporation technique	Improved solubility and stability	[49]
	Glutaric acid			

### Drug-drug cocrystals (DDC)

Drug-drug cocrystals represent a novel class of solid forms comprising two or more active pharmaceutical ingredients (APIs). They present a promising solution to the challenges associated with traditional combination therapies. DDCs offer potential as a solid-state platform for dual drug delivery, altering the physicochemical properties of constituent medications. Compared to other combination approaches, DDC technology can enhance API characteristics such as bioavailability, stability, and lifecycle management while potentially improving dissolution rates [50].

In a study by Carmen [51], a cocrystal of celecoxib (CTC) and tramadol hydrochloride was examined. Dissolution trials revealed a slower release of tramadol hydrochloride and an increased intrinsic dissolution rate (IDR) of celecoxib in the cocrystal. Comparative pharmacokinetic analysis with open combinations and single-entity reference products showed a favourable change in clinical profile. Celecoxib was absorbed more rapidly from CTC than tramadol, resulting in a decreased peak plasma concentration (C<sub>max</sub>). Phase II clinical trials demonstrated superior analgesic efficacy of CTC over tramadol and celecoxib in treating moderate to severe pain post-dental extraction involving bone removal. Additionally, this DDC formulation offers additional intellectual property protection, potentially extending the patent life of both tramadol and celecoxib.

### CONCLUSION

In recent years, cocrystals have garnered significant attention from scientists owing to their perceived low risk, affordability, and multifaceted advantages. Despite this, the body of research literature on cocrystal remains relatively sparse, and commercially available cocrystal are in short supply. Pharmaceutical researchers face challenges in predicting cocrystal development, understanding supramolecular interactions, and elucidating cocrystal association and dissociation patterns. Overcoming these challenges requires the development of novel crystallization technologies and more efficient screening protocols. Additionally, expanding cocrystals to include drug-nutraceutical combinations could unlock new possibilities for drug combinations and innovative medication applications. This exploration has explored various formulation strategies and therapeutic implications, highlighting the potential of cocrystals to enhance drug solubility, bioavailability, and stability, thus pushing the boundaries of conventional pharmaceutical formulations.

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### AUTHORS CONTRIBUTIONS

All authors have contributed equally

### CONFLICT OF INTERESTS

Declared none

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