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Review Article

Leveraging Co-crystallization to Enhance Therapeutic Potential of Anticancer Drugs

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ABSTRACT

Pharmaceutical co-crystals incorporating a minimum of one active pharmaceutical ingredient (API) remain a significant area of interest for investigators, particularly in the field of anticancer drugs. Co-crystals are formed via the non-covalent association of two or more distinct drug molecules. Co-crystallization is a process that can significantly improve several physicochemical characteristics, such as bioactivity, stability, solubility, and compressibility. This review focuses on co-crystals containing anticancer drugs reported in the literature, examining their physicochemical properties like permeability, solubility, stability, dissolution, bioavailability, and antitumor efficacy compared to the parent compounds. Although few publications specifically address the impact of anticancer co-crystals on drug resistance, there is a critical need for ongoing research in this area. The rising issue of drug resistance in cancer treatment underscores the importance of leveraging co-crystal technology to develop more effective therapeutic options. This review highlights, categorizes, and compares existing studies on anticancer drug co-crystals and encourages future research to explore their potential in overcoming drug resistance.

Introduction

In 2024, a total of nearly 2 million new cancer cases were reported, alongside 611,720 cancer-related deaths. Projections suggest newer cases of cancer may reach up to 35 million by the year 2050.[1] Current cancer treatments encompass surgery, radiation, and chemotherapy, often employed in combination. The non-selective nature of these agents causes collateral damage to healthy tissues with high cell turnover, resulting in severe toxic effects. Also, chemotherapy faces challenges like the rapid development of drug resistance, instability at the molecular level, and low aqueous solubility, which hampers cell membrane permeability.[2] Given the limitations and adverse side effects associated with conventional anticancer therapies, there is a pressing need to develop substitutes for the treatments that offer improved therapeutic efficacy with reduced toxicity.[3]

Since the early 2000s, the co-crystals have marked significant progress, culminating in the release of the very first marketable co-crystal product named Entresto by Novartis in 2015.[4] Pharmaceutical co-crystals have shown considerable potential in boosting the pharmacokinetic and physicochemical properties of drug substances over the last ten years.[5]

These co-crystals result from combining a drug molecule, present in molecular or ionic form, with a solid co-former. The overall mechanism by which co-crystallization enhances the therapeutic and physicochemical properties of anticancer drugs is depicted in Fig. 1.

The FDA released guidelines that define standards for how pharmaceutical co-crystals are developed and tested. These guidelines support their evaluation and regulatory approval.

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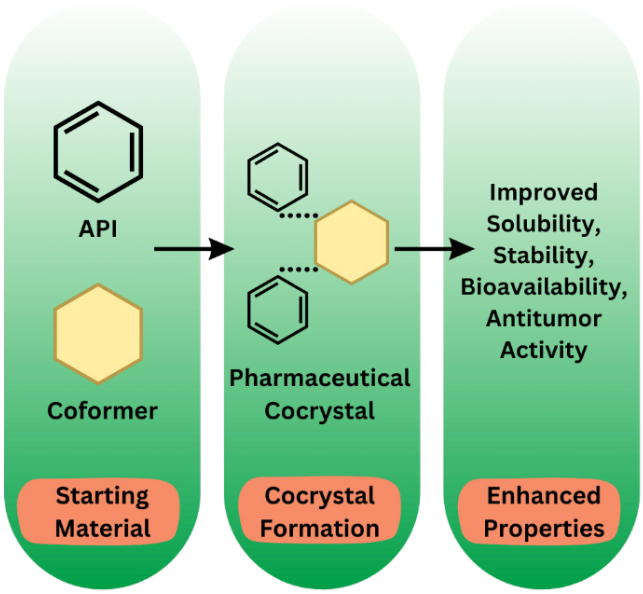

Fig. 1: Schematic representation of co-crystallization improving physicochemical and therapeutic performance of anticancer drugs.

Methods

Data Sources

Relevant literature was identified through searches in commonly used scientific databases, including PubMed, Scopus, Web of Science, Google Scholar. From these sources searches were conducted up to June 2025. Additional references were located by screening the bibliographies of key articles.

Search Strategy

Search terms related to pharmaceutical co-crystals and anticancer drugs were combined in different ways. Terms included co-crystal, pharmaceutical co-crystal, crystal engineering, anticancer, solubility enhancement, bioavailability, and drug resistance.

Study Selection

Articles were included if they described the preparation, characterization, or evaluation of co-crystals containing an anticancer drug. Studies comparing physicochemical or therapeutic properties of co-crystals with the parent drug were also included. Review papers without original data were used only for background understanding. Studies not involving anticancer APIs or not reporting measurable properties were excluded.

Data Extraction

For each eligible study, the following information was gathered when available: drug name, coformer used, method of co-crystallization, structural characteristics, and observed improvements in solubility, dissolution, stability, permeability, bioavailability, or anticancer activity. Information was summarized qualitatively due to variability in experimental approaches across studies.

Results

Stages and General Methods for the Development of Co-Crystals of APIs/Chemical Agents

A new co-crystal development involves three main stages before the conclusive approval. The first stage focuses on the selection of a suitable coformer and the experimental screening of potential co-crystals. The second stage centers on evaluating preclinical behavior and the solid-state properties of the co-crystals. The final and third stage covers the formulation and process scale-up to confirm that the co-crystal is suitable for mass production on a commercial scale.[6]

In the preparation of the co-crystals, co-former selection and experimental screening are critical steps. The selection of co-formers can be guided by several methods. Supramolecular compatibility, often determined using the Cambridge Structural Database or Hansen solubility parameters, is one such method. Polarity and Shape analyses, focusing on the polarity and shape of the API and co-former, are also employed. Lattice energy calculations based on methods for minimizing the energy and simulated co-crystal screening using molecular electrostatic potential surfaces provide valuable insights. The conductor-like screening model, based on fluid-phase thermodynamics theory, is another advanced method for selecting a co-former.[7] The sequential stages involved in pharmaceutical co-crystal design, characterization, and formulation are summarized in Fig. 2.

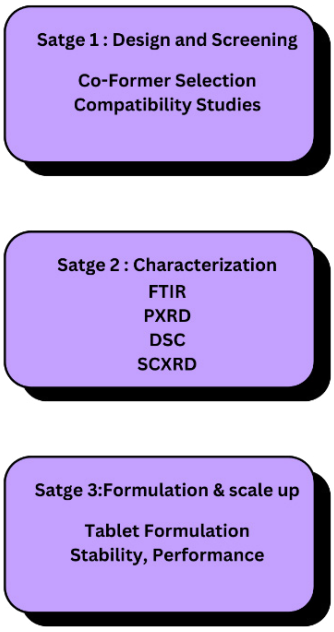

Fig. 2: Overview of key stages involved in the design, screening, and development of pharmaceutical co-crystals

In the case of co-crystals, all necessary experimental screening technology is readily available. The most widely employed and economical technique continues to be solvent evaporation. Multiple approaches support solution co-crystallization. These include temperature reduction, anti-solvent addition, slurry conversion, ultrasound-driven crystallization, and microwave-based crystallization. Another common approach is mechanical grinding, which can be performed either neat or with the assistance of a solvent. Supercritical fluid technology utilizes supercritical solvents for co-crystallization. Promising techniques for producing co-crystals on a large scale include high-shear granulation and spray drying.

Simultaneous thermal and spectroscopic analysis is made possible by advanced analytical methods, such as DSC-FTIR micro-spectroscopy, aiding in the screening process. High-throughput technologies, incorporating *in-situ* Raman microscopy, offer higher efficacy. These methods collectively enable the efficient preparation and screening of pharmaceutical co-crystals, enhancing the drug development process.[8]

Co-crystals of Anti-cancerous Therapeutic Agents

Multiple anticancer drugs share the general problem of low water solubility. The current target-based drug discovery approach often disregards the physicochemical properties of drugs, particularly their water solubility.[9-10] Consequently, many promising anticancer drug candidates, due to their poor water solubility, fail during clinical development itself. The crystalline form of drugs, while stable and pure, often contributes to poor solubility due to the high lattice energy barrier. Thus, poor water solubility remains an intrinsic challenge in the development of effective anticancer drugs.[11,12]

Oral anticancer drugs were investigated & classified into different categories based on the approaches of their formulation and Biopharmaceutical Classification System (BCS) class in a survey conducted by Sawicki *et al*.[13] The conclusions from the study, revealed that about 65% of these anticancer drugs exhibit poor water solubility, causing them to be categorized as either Biopharmaceutical Classification System (BCS) Class II or Class IV. This observation accentuates a critical gap in the ideal delivery of orally administered anticancer drugs to the desired site, as poor solubility often leads to suboptimal bioavailability and therapeutic efficacy.

Co-crystallization offers many advantages over other techniques, such as salts, solvates, and solid dispersions. Physicochemical properties of APIs can be enhanced through the use of co-crystals, including the drugs that are non-ionizable, and can be designed with a variety of non-toxic counter-molecules, unlike salts, which are limited by the need for a specific pKa difference. Co-crystals provide greater stability compared to solvates, which are often unstable and prone to desolvation. Unlike solid dispersions, which may crystallize upon storage and have limited application due to their metastable nature, co-crystals offer a more stable and versatile approach. [14]

Certain co-crystals have demonstrated improved solubility, leading to better therapeutic efficacy and enhanced anticancer properties compared to the original drug. The co-crystal of genistein and 4,4'-bipyridine has been reported to exhibit enhanced solubility and anticancer efficacy compared to genistein alone.[15]

This work aims to consolidate all studies on anticancer drug co-crystals to date, focusing on their structures, preparation methods, physicochemical property modifications, and their efficacy in overcoming drug resistance compared to the parent anticancer drugs. The summarized data on reported anticancer drug co-crystals and their improved properties are presented in Table 1.

We are going to discuss chronological development in this regard by taking various classes of anti-cancerous agents into consideration.

Antimetabolites

5-Fluorouracil[16-22]

5-Fluorouracil is a widely used drug of anticancer class, recent studies have explored its co-crystallization with various coformers to improve its physicochemical properties and anticancer efficacy. A notable advancement was made by cocrystallizing 5-FU with ferulic acid (FR). Consequently, the required dosage of 5-FU is lowered, which also reduces the risk of potential toxic side effects. Further studies have synthesized 5-FU co-crystals with cinnamic acid, succinic acid, malic acid, benzoic acid using slow evaporation and solid-state grinding methods. The anticancer activity of these co-crystals, particularly the 5-FU-cinnamic acid co-crystal, demonstrated a significantly higher potential for growth inhibition compared to the pure 5-FU.

There is another study in which the co-crystals of 5-FU were prepared with acetanilide, aspirin, urea, and thiourea, some of the pharmacologically safe coformers. The analyses revealed structural differences between the co-crystals and pure 5-FU. Apart from these, GRAS (Generally Recognized as Safe) coformers such as 3,4-dihydroxybenzoic acid, gentisic acid, and 4-aminopyridine were also used for the preparation of 5-FU co-crystals.

6-Mercaptopurine monohydrate [23-24]

6-Mercaptopurine monohydrate is an anticancer drug which is better known for having a lower oral bioavailability. To enhance its solubility, researchers have developed several co-crystals and salts with various coformers. Two notable co-crystals were formed with 4-hydroxybenzoic acid and 2,4-dihydroxybenzoic acid. The analysis revealed an intricate hydrogen bond network, involving interactions such as pyrimidine···carboxyl, pyrimidine···imidazole, carboxyl···Sulphur, and piperazine···imidazole. These

Table 1: Summary of enhanced properties of anticancer drugs via co-crystallization techniques

Drug	*Coformer(s)*	*Co-crystallization approach*	*Solubility outcome*	*Permeability outcome*	*Stability behavior*	*Dissolution result*	*Bioavailability effect*	*Antitumor response*	*Ref*
Alkylating agents									
Temozolomide	Succinic acid, Oxalic acid	SE	Increase reported	No change	Improvement reported	Increase reported	Improvement reported	Not reported	[46]
Antimetabolites									
5-Fluorouracil	Thiourea, Urea, Acetanilide	SG	Increase reported	No change	No improvement	No change	No improvement	No improvement	[16]
5-Fluorouracil	Thiourea, Urea, Pyrazinamide	SST	Increase reported	No change	No improvement	No change	No improvement	No improvement	[17]
5-Fluorouracil	Malic acid, Succinic acid, Benzoic acid, Cinnamic acid	GM, SSE	No improvement	No change	No improvement	No change	No improvement	Increase reported	[18]
5-Fluorouracil	Proline	LAG, SE	Increase reported	Increase reported	No improvement	No change	No improvement	No improvement	[19]
5-Fluorouracil	Iso-nicotinamide, Nicotinamide	GWOS	Increase reported	No change	Increase reported	No change	No improvement	No improvement	[20]
5-Fluorouracil	4-Aminopyridine, 3,4-Dihydroxybenzoic acid, Gentisic acid	SSG, SC	No improvement	Increase reported	No improvement	No change	No improvement	Increase reported	[21]
5-Fluorouracil	Ferulic acid	GWS	Increase reported	Increase reported	No improvement	No change	No improvement	No improvement	[22]
6-Mercaptopurine monohydrate	Zinc trifluoromethane sulfonate	SE	Increase reported	No change	No improvement	Increase reported	No improvement	No improvement	[23]
6-Mercaptopurine monohydrate	Hydroxybenzoic acid, 2,4-Dihydroxybenzoic acid	SRC	Increase reported	No change	Improvement reported	No change	No improvement	No improvement	[24]
Tegafur	p-Nitrophenol, 2,4-Dihydroxybenzoic acid	SS	Increase reported	No change	Improvement reported	Increase reported	Improvement reported	No improvement	[25]
Tegafur	Syringic acid	SE, LAG	No improvement	No change	No improvement	No change	Improvement reported	No improvement	[25]
Hormone therapies									
Megestrol acetate	Saccharin	SSE	No improvement	No change	No improvement	Increase reported	No improvement	No improvement	[53]
Nandrolone	Salicylic acid	GM	No improvement	No change	No improvement	No change	No improvement	Increase reported	[54]
Nandrolone	3-Amino-1,2,4-triazole	SR	No improvement	No change	No improvement	No change	No improvement	Increase reported	[54]

Immunomodulatory drugs									
Lenalidomide	Urea, 3,5-Dihydroxybenzoic acid	SE	Increase reported	No change	No improvement	No change	No improvement	No improvement	[41]
Lenalidomide	Gallic acid	LAG	Increase reported	No change	Improvement reported	No change	No improvement	No improvement	[42]
Natural products and derivatives									
Baicalein	Nicotinamide	SM	Increase reported	No change	No improvement	Increase reported	Improvement reported	No improvement	[33]
Betulinic acid	Ascorbic acid	SSE	Increase reported	No change	No improvement	No change	Improvement reported	No improvement	[34]
Coumarin	Thiourea	NG	Increase reported	No change	No improvement	No change	No improvement	Increase reported	[48]
Curcumin	N-acetylcysteine	SCF	No improvement	No change	No improvement	No change	Improvement reported	No improvement	[35]
Curcumin	Trimesic acid	SCM, SG, EC	No improvement	No change	No improvement	Increase reported	No improvement	No improvement	[36]
Curcumin	Ascorbic acid	SE	Increase reported	No change	Improvement reported	No change	No improvement	Increase reported	[37]
Curcumin	N-acetylcysteine	SCF	Increase reported	No change	No improvement	Increase reported	No improvement	No improvement	[38]
Emodin	Nicotinamide	SE	Increase reported	No change	No improvement	No change	Improvement reported	No improvement	[49]
Lapachone	Resorcinol	MG	Increase reported	No change	No improvement	No change	Improvement reported	No improvement	[50]
Luteolin	Caffeine	LAG, RSRM	Increase reported	No change	Improvement reported	No change	Improvement reported	No improvement	[51]
Resveratrol	Nicotinamide	GAS	No improvement	No change	No improvement	Increase reported	Improvement reported	No improvement	[52]
Taxanes									
Docetaxel	Nicotinamide	SSE	Increase reported	No change	No improvement	Increase reported	No improvement	No improvement	[40]
Tyrosine kinase inhibitors (TKIs)									
Axitinib	Fumaric acid, Cinnamic acid	LAG, SMs	Increase reported	No change	Improvement reported	No change	Improvement reported	No improvement	[27]
Axitinib	Glutaric acid	SE	Increase reported	No change	Improvement reported	No change	No improvement	No improvement	[28]

Dabrafenib	Succinic acid, Fumaric acid, Adipic acid	SDG	Increase reported	No change	No improvement	Increase reported	No improvement	No improvement	[29]
Dasatinib	Nicotinamide, N-methyl-4-hydroxybenzoate, Methyl gallate, Ethyl gallate, Propyl gallate, Vanillin	SE	Increase reported	No change	Improvement reported	No change	Improvement reported	No improvement	[30]
Dasatinib	4-Chlorobenzoic acid, 4-Hydroxybenzoic acid, Sorbic acid	SEA	Increase reported	No change	No improvement	No change	No improvement	No improvement	[31]
Gefitinib	Isonicotinamide, Vanillin	SE	No improvement	No change	Improvement reported	No change	Improvement reported	Increase reported	[32]
Imatinib	Syringic acid	SM	Increase reported	No change	No improvement	Increase reported	No improvement	No improvement	[43]
Ibrutinib	Succinic acid, Hydroxybenzoic acid, Hydroxynaphthoic acid	SM, US	Increase reported	No change	Improvement reported	No change	No improvement	No improvement	[44]
Lenvatinib	Salicylic acid	SSE	Increase reported	No change	Improvement reported	No change	No improvement	No improvement	[45]
Lenvatinib	Sulfamerazine, Salicylic acid	SRC	Increase reported	No change	Improvement reported	Increase reported	No improvement	No improvement	[45]
Lenvatinib	Sulfamerazine	SSE	Increase reported	No change	Improvement reported	No change	No improvement	No improvement	[45]
Palbociclib	Orcinol	SE	Increase reported	No change	No improvement	Increase reported	No improvement	No improvement	[46]
Palbociclib	Resorcinol	SE	Increase reported	No change	No improvement	No change	Improvement reported	No improvement	[46]
Regorafenib	Glutaric acid, Malonic acid, Pimelic acid	LAG	Increase reported	No change	No improvement	Increase reported	No improvement	No improvement	[47]

Abbreviations: SG, solid-state grinding. LAG, liquid-assisted grinding. SSG, Solvent-assisted grinding. SE, solvent evaporation. SSE, Slow solvent evaporation. SM, slurry method. SRC, slurry reactive crystallization. SCF, supercritical fluid technique. SST, Supercritical solvent technique. GAS, gas antisolvent technique. SCM, slow cooling crystallization. MG, mechanical grinding. US, ultrasonic-assisted crystallization. SS, solid-state synthesis. SDG, solvent drop grinding. RSRM, rapid solvent removal methods. SR, solution reflux. GWOS, Grinding without Solvent. SC, solution crystallization. GWS, Grinding with Solvent. GM, Grinding method. EC, Evaporative crystallization. SEA, Slow evaporation approach. NG, Neat grinding.

new solid forms significantly improved the solubility of the drug in phosphate buffer at a pH of 6.8. In another study, two ionic co-crystals of 6-Mercaptopurine monohydrate were synthesized with zinc trifluoro methane sulfonate (Zn(CF3SO3)2). The prepared crystal forms lead to the enhanced solubility and dissolution rates of 6-mercaptopurine.

Tegafur[25-26]

In 2020, to enhance the biopharmaceutical characteristics of tegafur, A novel supramolecular adduct comprising tegafur (TF) with syringic acid (SYA) was developed, which also optimized the pharmacokinetic characteristics of TF. TF-SYA co-crystals were evaluated for solubility and permeability under various physiological pH conditions. It was found that the TF-SYA co-crystal has significantly improved water solubility and permeability compared to pure TF.

Two novel 1:1 co-crystals of TF were prepared using p-nitrophenol and 2,4-dihydroxybenzoic acid as coformers. The goal was to overcome the drug's low water solubility, which limits bioavailability. High-performance liquid chromatography was used to evaluate solubility and dissolution behavior. The TF–2,4-dihydroxybenzoic acid co-crystal showed a clear rise in both dissolution rate and solubility when compared with unmodified TF. All prepared co-crystals remained stable for eight weeks under accelerated storage conditions.

Tyrosine Kinase Inhibitors (TKIs)

Axitinib[27-28]

Two co-crystals of axitinib (AXI) have been described with glutaric acid (GA). Their characteristics were investigated. AXI-GA I is found to be the most stable form thermodynamically. This form demonstrated significantly improved solubility while maintaining sufficient stability. Co-crystallization of axitinib with carboxylic acids as coformers was explored, resulting in the formation of one salt co-crystal having fumaric acid as a coformer, along with a dual molecular co-crystal having trans-cinnamic acid and suberic acid as coformers. The newly formed co-crystals showed enhanced dissolution rates and solubility in comparison to the pure drug, without compromising its physical stability.

Dabrafenib[29]

Dabrafenib (DBF), a targeted anticancer agent. Though, because it has low aqueous solubility, DBF is categorized as a BCS Class II drug. To overcome this constraint, numerous salts and co-crystals were explored using GRAS. Conversely, succinic acid (FA), fumaric acid (SA), and adipic acid (ADA) yielded co-crystals.

Dissolution studies conducted at pH 1.2 showed that co-crystals of dabrafenib with ethylenediamine had a significantly faster dissolution rate compared to DBF·MS. Cytotoxicity assays confirmed that DBF·EN⊃H2O was non-toxic to normal cells while maintaining comparable potency against cancer cells to that of DBF and DBF·MS.

Dasatinib[30-31]

The development of co-crystals of dasatinib is likely to be with the primary goal of enhancing its aqueous solubility. Dasatinib (DAS) has been subjected to co-crystallization techniques to improve its physicochemical properties in another study. Three novel DAS co-crystals were synthesized using the slow evaporation method, using coformers like 4-chlorobenzoic acid, sorbic acid and 4-hydroxybenzoic acid. DAS co-crystals demonstrated significantly enhanced solubility when compared to the parent DAS drug.

Gefitinib[32]

Gefitinib (GEF), was recently involved in the 2023 reporting of two new co-crystals. These co-crystals of GEF were developed using GRAS coformers: vanillin (VAN) and isonicotinamide (INCT). Co-crystals were synthesized and showed improved intrinsic dissolution rates, higher maximal serum concentrations, and enhanced inhibition of cell responses when compared to the pure drug. The GEF-INCT·2H2O co-crystal outperformed GEF-VAN.

Natural Products and Derivatives

Baicalein[33]

Baicalein (BE) is a prominent flavonoid. In a study Baicalein-nicotinamide (BE-NCT) nano-cocrystals were synthesized using high-pressure homogenization. Dissolution tests indicated that the newly synthesized nano-cocrystals showed an upsurge in dissolution rates compared to the BE powder. Oral administration studies exhibited a significant improvement in bioavailability.

Betulinic acid [34]

Betulinic acid is a promising anticancer agent. In a study, researchers successfully attained co-crystals of BA with a coformer ascorbic acid (BA+Vit C). Notably, these co-crystals exhibited an additive antioxidant effect. The results established that the co-crystallization of BA with vitamin C led to a superior cytotoxic effect on the tested tumor cell lines, while sustaining a good selectivity index.

Curcumin [35-38]

Curcumin (CUR) is a bioactive compound. However, its application in the pharmaceutical and food sectors is significantly hampered by poor aqueous solubility and low bioavailability. In a study, a novel co-crystal with curcumin-ascorbic acid was developed with the aim of improving the solubility, stability, and complementary biological activities of curcumin. For this study, ascorbic acid was identified as a suitable coformer, and via the solvent evaporation method, the co-crystals were prepared. The resulting co-crystals demonstrated a

remarkable enhancement in aqueous solubility, compared to simple curcumin. The dissolution rate of the curcumin co-crystal with-ascorbic acid was also superior.

Another study focused on the co-crystallization of curcumin with trimesic acid (TMA). These were evaluated for cytotoxicity and cell invasion. The results showed that all curcumin multicomponent solid forms, showed improved bioavailability compared to unprocessed curcumin.

Supercritical solvent (CSS) techniques have been investigated for co-crystallization as a means to enhance curcumin's water dissolution rate. For example, in one investigation, N-acetylcysteine (NAC) was chosen as a coformer. Notably, these co-crystals demonstrated a significant enhancement in performance, exhibiting a 2.2-fold increase in their dissolution rate in water compared to pure curcumin.

Alkylating Agents

Temozolomide[39]

The co-crystals of temozolomide formed using organic acids as a coformer demonstrated greater stability under physiological conditions compared to the standard drug. Specifically, the half-life (T1/2) of temozolomide co-crystals with salicylic and oxalic acid, measured via UV-Visible spectroscopy in a pH 7 buffer, was found to be twice as long as that of pure temozolomide. Similarly, co-crystals of temozolomide with tartaric acid, malic acid, and succinic acid exhibited prolonged half-lives. Stability tests, conducted in accordance with ICH guidelines at 40°C and 75% relative humidity, demonstrated a significant difference between temozolomide and its co-crystals. Specifically, the hydrolytic degradation of solid temozolomide began after just one week, as evidenced by PXRD analysis. In contrast, the co-crystals formed with oxalic acid and succinic acid as coformers maintained their integrity for an extended period of up to 28 weeks, clearly highlighting the superior stability of the co-crystals compared to the parent drug. The intrinsic dissolution rates of temozolomide co-crystals, specifically those formed with oxalic acid and succinic acid, were similar to that of pure temozolomide when measured in a pH 7 buffer, among all the examined temozolomide co-crystals, the ones that are prepared using oxalic acid and succinic acid as coformers displayed both improved stability and dissolution rates similar to the standard drug.

Taxanes

Docetaxel[40]

Docetaxel (DTX) is recognized as the most potent drug for cancer treatment. Its therapeutic promise faces barriers in practice because of low solubility and high lipophilicity. To overcome these issues, nicotinamide (NCT) served as a co former in the design of a docetaxel nicotinamide (DN) complex. The stability of this complex was confirmed through various studies. It shows improved solubility and dissolution as compared to API alone.

Immunomodulatory Drugs

Lenalidomide[41-42]

To overcome poor oral bioavailability, lenalidomide was formulated as co-crystals with urea and 3,5-dihydroxybenzoic acid. Single-crystal X-ray diffraction showed the formation of three-dimensional hydrogen-bonded networks. This structural organization led to higher solubility and a faster intrinsic dissolution rate of lenalidomide in pH 6.8 phosphate buffer. Notably, two of these co-crystals can interconvert under certain conditions, indicating a dynamic equilibrium in their solid-state forms.

Two co-crystals of lenalidomide with gallic acid were developed, demonstrating improved intrinsic dissolution rates and sustained high solubility for up to 48 hours. The phase solubility study revealed that gallic acid forms a stable 1:1 complex with lenalidomide in aqueous solution, attributed to multiple hydrogen bonding interactions. This complex formation is crucial for maintaining the consistent high solubility of the co-crystals.

Conclusion

Co-crystallization has emerged as a practical approach to address long-standing limitations of many anticancer drugs, especially those with poor solubility, unstable solid forms, or low oral bioavailability. The studies reviewed here show that suitable coformers and carefully selected crystallization methods can produce solid forms with improved dissolution behavior, stability, permeability, and, in several cases, enhanced anticancer activity. Although the available literature demonstrates meaningful progress, most reports focus only on physicochemical improvements, while the effect of co-crystals on drug resistance, long-term safety, and clinical relevance remains insufficiently explored. Future work should include systematic comparisons across drug classes, deeper mechanistic evaluation, and broader biological testing. Continued research in this direction can support the development of more reliable and effective anticancer therapies based on co-crystal design.

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