

Review

Cocrystals and Drug–Drug Cocrystals of Anticancer Drugs: A Perception towards Screening Techniques, Preparation, and Enhancement of Drug Properties

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Abstract: The most favored approach for drug administration is the oral route. Several anticancer drugs come under this category and mostly lack solubility and oral bioavailability, which are the most common causes of inadequate clinical efficiency. Enhancing oral absorption of anticancer drugs with low aqueous solubility and drug impermeability is currently an effective area of research. Many scientists have looked into pharmaceutical cocrystals as a way to improve the physicochemical properties of several anticancer drugs. Benefits of pharmaceutical cocrystals over other solid forms may include improved solubility, bioavailability, and a reduced susceptibility for phase transition. Cocrystal strategy also stands as a green synthesis tool by using very limited organic solvents during its formulation. Having so many advantages, to date, the reported cocrystals and drug–drug cocrystals of anticancer drugs are limited. Here we review the pharmaceutical cocrystals and drug–drug cocrystals of the anticancer drugs reported in the last decade and their future in imaging, and also shed light on the opportunities and challenges for the development of anticancer drug cocrystals.



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1. Introduction

Cancer is regarded as one of the prevailing and major reasons for increased death worldwide and creating a huge global public health concern [1]. Cancer is one of the leading reasons for death, standing second globally with one in six deaths [2]. In accordance with the Global Cancer Observatory (GCO), an estimated nineteen million new instances and ten million deaths from cancer occurred in 2020 [3]. Even though these impressive numbers are testimony that the “war on cancer” has not been won [4], by the next decade, the projected global load is likely to rise to three billion additional cases and sixteen million deaths from cancer [5].

There are different types of cancers out of which a few occurring kinds are colorectal cancer, endometrial cancer, lung cancer, kidney cancer, bladder cancer, leukaemia, pancreatic cancer, melanoma, prostate cancer, breast cancer, non-Hodgkin lymphoma, uterine cancer, skin cancer, liver cancer, thyroid cancer [6]. The facts and statistics of several cancers are depicted in Figure 1.

Over the last decade, due to intensified prevalence of cancer, it has been a challenge for health workers [7]. The discipline of science and technology has continuously been working on gaps in its field and witnessed tremendous relative growth in filling the gaps related to drug therapies [8]. Until the previous few decades, most of the cancer treatment was administered solely through the parenteral route. Nevertheless, considering the ease and frequency of dose administration, when compared to the parenteral route, the oral route has attracted a lot of attention [9].

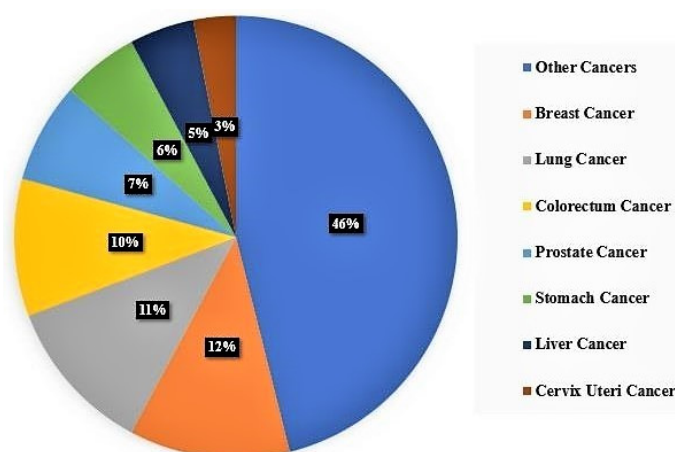


Figure 1. Facts and Statistics of several cancers.

The oral route of administration is one of the most common and conventional methods for drug delivery; with the major benefits of improved safety, comfort, and patient acceptance [10]. The ability to create customized formulations based on the physicochemical attributes of drug substances stands appealing to the scientific community. However, due to extensive first-pass effect, lower aqueous solubility, higher efflux ratio, impermeability, and bioavailability, oral administration of cancer chemotherapeutic agents is hampered [11].

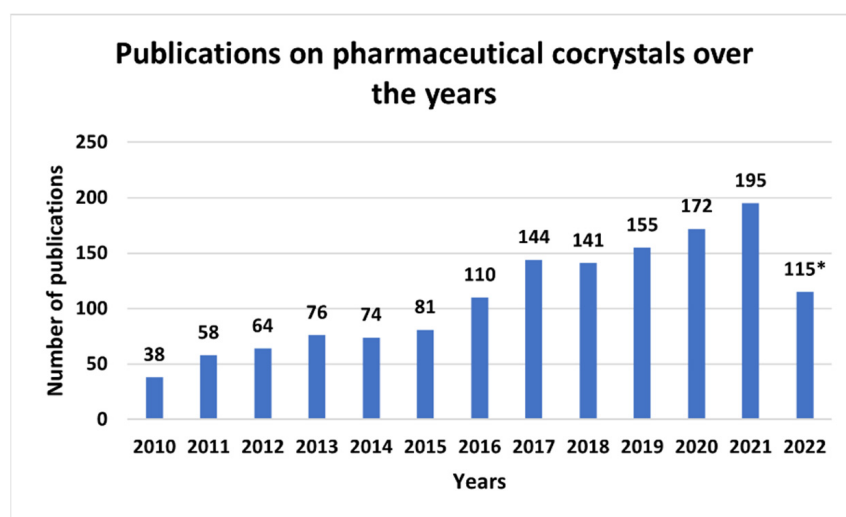
About 75% of new chemical entities (NCEs), notably anticancer drugs, are believed to be highly water-insoluble molecules [12]. Aqueous solubility stands as a major roadblock to the development and clinical application of these anticancer agents. “According to the Biopharmaceutics Classification System (BCS), a drug is considered to be poorly water-soluble if its highest dose strength is not soluble in 250 mL or less of aqueous media over the pH range of 1 to 7.4” [13]. Unfortunately, many anticancer drugs fall into BCS class 2 and 4 with low solubility, for example, curcumin [14], paclitaxel [15], dasatinib [16], docetaxel [17] and many have a promising antineoplastic activity, which falls into this category. These drugs usually have high lattice energies which restrict the drug from dissolving and form hydrogen bonds with water [18], further restricting the solubility typically below the microgram per milliliter range.

Over the past few decades, many efforts have been made to resolve the lower solubility issues and also improve the drug properties via various novel formulations such as amorphous solid dispersions (ASDs) [19], complexation [20], lipid-based systems [21], nanoparticles [22], and crystal engineering [23], as well as the application of new technologies such as hot-melt extrusion [24], spray-drying [25] and other hybridization technologies [26] to circumvent solubility, dissolution rate, and bioavailability problems of poorly aqueous soluble drugs [27]. Each of these formulation systems has its cons of instability, moisture uptake, poor scale-up, high methodology cost, thermal instability, and other excipient incompatibilities. Especially, though ASDs success rate in enhancing the solubility is higher than the cocrystals, their lack of stability and recrystallization always stands as a problem that clears way to form cocrystals when there is no such point for recrystallization.

Since oral administration is the most convenient route of administration; solid dosage forms, such as tablets and capsules, account for more than 80% of commercial pharmaceuticals [28]. Polymorphs, amorphous forms, cocrystals, salts, and their hydrates can be employed to change the physicochemical properties of drugs for solid-state formulations [29]. The processing, distribution, and therapeutic effectiveness of any dosage form are all influenced by the physicochemical parameters of active pharmaceutical ingredients (APIs), such as stability, dissolution, hygroscopicity, and solubility [30]. There is still so much scope for the breakthrough of desirable stable forms of an API for clinical application by changing just the physicochemical properties without disrupting the molecular-level chemical form of the API where cocrystals and salts are the best suited for justification.

The most promising method for increasing API solubility and dissolution is salt formation [31]. Salts, on the other hand, have the disadvantage of being more likely to form hydrates over cocrystals, and many have a high hygroscopicity, rendering them susceptible to deliquescence upon water sorption [32].

Cocrystallization has increased interest in recent years, and as mentioned in Figure 2, proves to be one of the approaches to improve the bioavailability of water-insoluble drugs [33].



* More publications under process

Figure 2. Publications on pharmaceutical cocrystals over the years.

Unlike salts, non-ionizable drugs can benefit from cocrystallization [34]. Cocrystals do not have the physicochemical stability concerns that ASDs do due to their crystalline form as mentioned in Figure 3 [35].

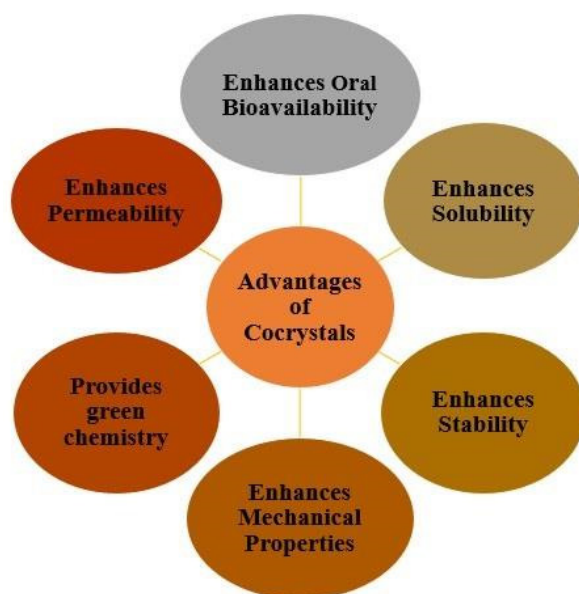


Figure 3. Advantages of pharmaceutical cocrystals.

In cocrystallization, with several advantages come various disadvantages, such as difficulty in scaling up, efficiency problems, may form solvates, issues during stability such as hydrolysis and not being appropriate for thermolabile drugs.

The main objective of this review is to highlight recent breakthroughs in enhancing the solubility, oral bioavailability, and efficacy of anticancer drugs via cocrystallization. Cocrystals of different anticancer drugs are studied in terms of their design, discovery, preparation, and characterization to demonstrate how these new crystalline forms can improve APIs characteristics. Additionally, new aspects of green synthesis and the advantages of imaging platforms through cocrystals have been discussed. Finally, we review the research on cocrystals of numerous anticancer drugs, concentrating on how many cocrystal frameworks could improve pharmacokinetic behavior.

2. Cocrystals for the Pharmaceutical Formulation Development

Pharmaceutical cocrystals are crystalline compounds that have two or more different molecules in their crystal lattice [36]. The benefits of cocrystals include their stable crystalline shape and do not include any other excipients [37]. The attributes that play a significant part in influencing physicochemical characteristics include the properties of APIs and coformers [38].

As mentioned, pharmaceutical cocrystals may have several distinct advantages over all the other orally administered solid dosage forms and allow the highly efficacious small molecules that may disappear if all their drawbacks are not rectified [39]. Adding more light to its pharmaceutical cocrystals provides more prospects to the investigators by improving the lifespan of the dosage form as a part of its intellectual properties [40].

The low solubility of drugs in an aqueous medium leads to diminished bioavailability [41]. In this regard, several formulation techniques are available for enhancing the drug solubility or dissolution by their enhancement mechanisms, such as particle technology for increasing drug solubility using micronization, nanocarriers, crystal engineering, etc., [42]. As mentioned, cocrystals follow the spring and parachute effect, which enables the use of supersaturation as a strategy to increase the solubility and dissolution rate of poorly soluble APIs; however, two crucial processes must be maintained:

1. Formation of the supersaturated metastable state.
2. Maintaining the above condition.

Supersaturation of poorly water-soluble APIs can be achieved using a variety of approaches, which includes crystalline salts, cocrystals, ASD in polymers, metallic frameworks, and nanoparticles.

In general terms, drug bioavailability is directly proportional to the dissolution [43]. Most of the techniques such as ASDs, eutectics, and cocrystals follow the conceptual mechanism of the “spring and parachute effect” [44].

- (1) The solubility of the crystalline (stable) state is low.
- (2) The metastable form (amorphous) has a maximum solubility but rapidly decreases to the poorly soluble form (crystalline form).

Details regarding the “spring and parachute” effect are depicted in Figure 4, which explains the phenomenon of the “spring effect” where the drug dissolves immediately, creating a super saturation concentration, and most significantly, the supersaturated state, which is thermodynamically unstable has to persist for a comparatively extended time to ensure that the drug is absorbed effectively; this phenomenon is identified as the “parachute effect” [45]. In case the “parachute period” is rapid, the drug in its “spring stage” will precipitate quickly, resulting in reduced drug absorption [46]. As a result, the benefits of increased dissolution during the spring effect would be reduced, and simultaneously the APIs availability [47]. To constrict this precipitation and extend the parachute effect and avoid the precipitation of the unstable crystal forms, hydrophilic polymers such as HPMC, PVP, etc., can be added to inhibit precipitation [48]. They also add in synergism, which improves the dissolution, extends the parachute effect, and proportionally improves the absorption and bioavailability of cocrystals [49].

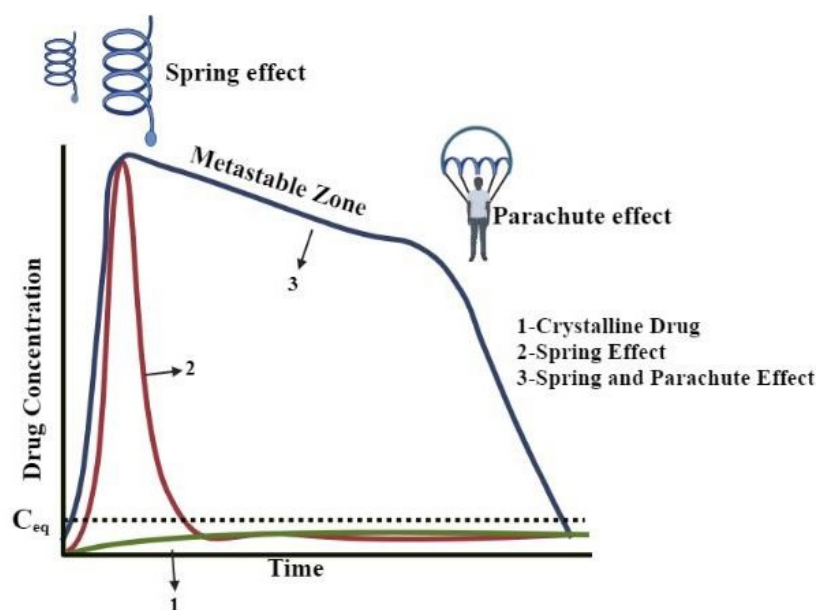


Figure 4. To generate higher apparent solubility for aqueous insoluble drugs, the spring and parachute idea was used.

3. Coformer Screening and Selection Techniques

Selecting the best suitable coformer stands as a crucial phase to accessing the cocrystals with suitable properties and simultaneously crystal engineering of APIs is a difficult task [50].

Since the range of coformers that should be evaluated often reaches hundreds and more than one method is frequently used to validate cocrystal generation, this makes the selection of acceptable coformers the most difficult phase in cocrystal development [51].

The basic concept for cocrystal production is supramolecular chemistry [52]. Most of the APIs and coformers possess intermolecular bonding moieties, the most common of which is hydrogen bonding [53]. Various screening procedures are used to determine the likelihood of supramolecular synthon formation between the binding sites of the drug and coformer [54], the experimental product is then synthesized and characterized to identify a successful hit. Cocrystal screening has had a lot of success, from using synthon matching to complicated Insilco coformer screening techniques [55].

Cocrystal screening approaches have evolved through time and can be divided into conceptual, in-silico, and practical methods [56]. Due to a dearth of research into the kinetics of cocrystallization, no single strategy assures cocrystal formation [57]. The data gathered through theory and in-silico methods aid in justifying the experimental procedure and fine-tuning the cocrystal's attributes [58].

3.1. Hypothetical/Theoretical Methods

The process of formulating cocrystals has been explained using several conceptual approaches such as “Hydrogen bonding propensity, Cambridge Structure Database, supramolecular synthon, pKa values, and Hansen solubility parameters”.

3.1.1. Hydrogen Bonding

The motif of hydrogen bonding synthons of cocrystals may be based on Etter's empirical hydrogen-bonding guidelines for designing the hydrogen-bonded solids [59].

Etter investigated the predictability of hydrogen bonding in known crystal structures and presented a set of empirical hydrogen-bonding principles that regulates the H-bond assembly of chemical compounds forming crystals [60]. Etter's three hydrogen-bonding principles are as follows:

- “All good proton donors and acceptors are used in hydrogen bonding”

- “Six-membered-ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bond”
- “The remaining best proton donors and acceptors, after intramolecular hydrogen-bond formation, form intermolecular hydrogen bonds with one another”

These guidelines assist in discovering excellent donor as well as acceptor groups and enable the development of multi-coformer cocrystals. This technique was effectively used by V J Nikam and his co-authors to identify the cofomers for nebivolol hydrochloride [61].

3.1.2. Supramolecular Synthons Approach

Noncovalent interactions between the drug and cofomers such as hydrogen bonding, van der Waals forces, and pi-pi stacking play a vital role in the formation of cocrystals [62].

In accordance with these guidelines, Desiraju [63] suggested the model of supramolecular synthons approach “Supramolecular synthons are structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions”.

Desiraju stated that “supramolecular synthons are robust entities and can be exchanged from one hydrogen bonding assembly to another”.

The following processes are involved in designing cocrystals utilizing hydrogen bonding laws and the supramolecular synthon approach:

- “Identification of functional groups in the API and cofomer molecules”.
- “Assessment of homo interactions in the individual pure molecules of the target compounds”.
- “Identification of the possible functional groups which may compete with the homo interactions of pure compounds”.
- “Assessment of the likelihood of hetero interactions”.
- “Selection of cofomers based on the assessment of homo/ hetero interactions”.

This technique was effectively used by Rajendrakumar S and co-workers in screening the cofomers for deferiprone [64].

Supramolecular synthons are divided into two types:

Supramolecular Homosynthon: Functions that are the same and complimentary.

Supramolecular Heterosynthons: Functions that are diverse yet complimentary.

The theory of the homo and hetero synthon approach is illustrated in Figure 5.

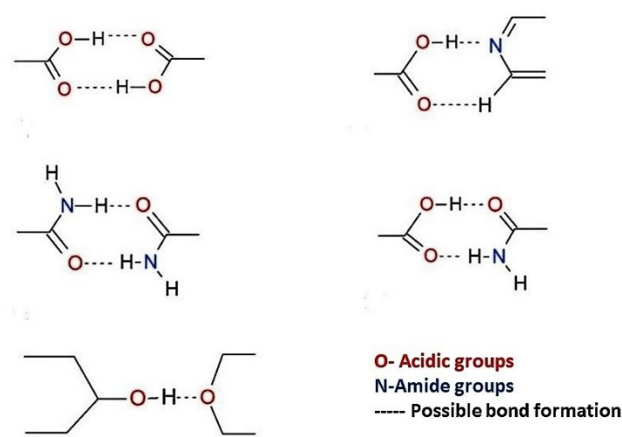


Figure 5. Common supramolecular synthons formed from carboxylic acids, amides, pyridines, and other aromatic nitrogen.

3.1.3. ΔpK_a Rule of Three

This rule states that “if the value of ΔpK_a is less than 0, the possibility of formation of cocrystal increases while, for the ΔpK_a differences greater than 3 will result in the formation of salts”. ΔpK_a within the range of 0 to 3 is defined to be a grey zone where no accurate prediction is possible [65].

The ΔpK_a value is estimated by using the equation given below:

$$\Delta pK_a = pK_a(\text{base}) - pK_a(\text{acid}) \quad (1)$$

The proton transfer possibility is determined by the ΔpK_a value obtained from the above equation.

Dos Santos et al. justified the ΔpK_a rule by exploring several coformers to prepare cocrystals of cinnamic acid and succeeded in improving the solubility of the low soluble trans-cinnamic acid [66]. Although the ΔpK_a rule can be used for preliminary screening, it is unlikely to be sufficient for cocrystal screening.

3.1.4. Hansen Solubility Parameter

Another theoretical strategy for screening cocrystals is the Hansen solubility parameter (HSP). According to HSP, “cocrystals are considered to be miscible systems, and the miscibility of API and coformer is supposed to be related to the solubility parameter (δ)”.

As a result, estimating the solubility parameter can give a good idea of cocrystallization possibilities. The solubility parameter can be determined using the formula:

$$\delta_t = (\delta^2 d + \delta^2 p + \delta^2 h) \quad (2)$$

where,

(δd) = Dispersion.

(δp) = Polarity.

(δh) = Hydrogen bonding.

In the literature, there are various examples of HSP being used as a cocrystal screening method [67,68].

3.2. In-Silico Techniques

Several in-silico approaches for screening cocrystals are now available and it has been possible due to better technologies and computer modelling techniques. There are a variety of strategies that may be utilized to properly forecast the production of cocrystals, which saves time and money in research and development.

3.2.1. Cambridge Structural Database (CSD)

The CSD is an important resource for determining intermolecular hydrogen bonding in crystals [69]. CSD is significant for the development in the field of chemical sciences, material sciences, and life sciences, as well as drug innovation and development. With roughly 40,000 new structures added each year, the CSD is a well-designed and efficient software [70].

CSD can also be used to forecast stable H-bond motifs, to maintain the strongest motifs throughout a set of core structures [71,72]. On the other hand, CSD also facilitates hydrogen bonding propensity (HBP), a tool for designing cocrystals [73].

To understand the behavior of molecules and intermolecular forces better within a crystal, CSD allows for the retrieval, visualization, and analysis of experimentally obtained crystallographic data. This provides details on the type of molecular interactions, geometrical alternatives, directional properties, and supramolecular synthon types involved [74].

According to Fabian’s method [75], CSD provides the most reliable cocrystal forming pairs where certain parameters are considered for every molecule, known as molecule descriptors, for example, polarity, molecular shape, size, dipole moment, a single atom, surface area, etc. The system database figures out the pairs of molecules which could develop pharmaceutical cocrystals on account of calculated molecular properties. The strongest and most effective descriptor correlation was associated with the polarity and shape of the coformers [76].

Statistical analysis using cocrystal datasets on CSD enables research groups to use virtual screening approaches to locate acceptable cocrystal forming combinations, further enabling cocrystals to be built using molecular modelling, saving both time and money [77].

3.2.2. Conductor-Like Screening Model for Real Solvents (COSMO-RS)

COSMO-RS is an alternative method that is growing in popularity as a high-performance virtual screening tool. This theory is a unique blend of quantum chemistry and solution-based thermodynamics. The difference in the residual enthalpies of both the individual components as well as the cocrystal is used to forecast the creation of the cocrystal phase, assuming interactions within the solid phase are comparable to those in the supercooled phase [78]. COSMO-RS is a high-throughput screening method that may be used for screening hydrates and assist the selection of optimal cocrystallization solvents [79]. Di Wu et al., explored the prospects of COSMO-RS with other models to calculate the cocrystal consequences of the host, 2-amino-4,6-dimethoxypyrimidine (MOP), with another 63 molecules and concluded that COSMO-RS was the most efficient and reliable technique with a total hit rate of 84.1% [80].

3.2.3. Molecular Electrostatic Potential Surface (MEPS)

The MEPS technique, which is closely similar to the COSMO-RS approach, focuses on theoretical concepts and experimental findings of intermolecular interactions in the gaseous phase rather than just the liquid phase employed in the COSMO-RS strategy. The MEPS technique considers Gibbs free energy, and while enthalpy and entropy are important for characterizing intermolecular interactions, determining them is a tough process since a tiny change in the system may have a large influence on the system's enthalpy and entropy, even though the shift in the free energy is very minimal. Free energy is regarded as a significant parameter to measure the intermolecular interactions [81]. Barbas et al., evaluated sildenafil and resorcinol using the MEPS approach for the successful formation of their cocrystals [82]. In another study Dezhi Yang et al., successfully determined the changes in the intermolecular interaction sites of three flavanols—explicitly, kaempferol, quercetin, and myricetin—with the cocrystal conformer praziquantel using MEPS and prospered in predicting the conformational changes occurring during the formation of cocrystals [83].

3.2.4. Lattice Energy Assessment

Another virtual screening approach that considers thermodynamic principles to forecast probable coformers is lattice energy [84]. The cocrystal phase is likely to be preferred when it is thermodynamically stable than the individual elements, i.e., the cocrystals' lattice energy should be greater than the individual elements [85].

Each molecule's lattice energy is calculated using Equation (3) as the sum of:

$$E_{latt} = U_{inter} + \Delta E_{intra} \quad (3)$$

where,

E_{latt} = Lattice energy.

U_{inter} = intermolecular lattice energy.

ΔE_{intra} = conformational intramolecular energy.

Greater the difference between the lattice energy of cocrystal and pure elements, the higher the probabilities of cocrystallization [86]. This method is not just restricted to neutral molecules but may be used to analyze salts, solvates, and other solid and liquid systems. Despite previous methods, this method makes no assumptions regarding hydrogen bonding [87].

3.3. Pick and Trial Approaches

Cocrystallization studies with small quantities of API and coformer are used for this experimental approach. Broadly, mechanochemical synthesis methods, for example neat

grinding and solvent-based grinding, are desired for screening coformers for cocrystals [88]. These approaches utilize kinetic energy as a tool for cocrystallization. Equimolar proportions containing API as well as coformer are co-grounded [89] for a predetermined length of time either using a ball mill or a mortar pestle [90].

Liquid-assisted grinding (LAG) uses a little quantity of any organic solvent to speed up the cocrystallization process [91]. Liquid-assisted grinding is often chosen over neat grinding due to its inherent benefits and a better success rate [92].

Several solution-based screening techniques, including grinding slurry and solution crystallization, are also used in addition to mechanochemical procedures [93].

The techniques described above have their own set of restrictions that are tough to overcome. Mechanochemical techniques may sometimes fail in developing cocrystals. The problem of finding a suitable solvent for cocrystallizing in a solution-based technique is a hurdle to overcome [94]. Additionally, it is impossible to exclude the occurrence of solvate/hydrates. Another noteworthy technique for cocrystallization is a cocktail method, where more than two coformers will be co-grounded with API, saving time and money [50,95].

3.4. Thermal Screening Techniques

Several thermal screening techniques, such as differential scanning calorimetry (DSC) [96], and Hot Stage Microscopy (HSM) [97], provide a quick, time- and money-saving technique for selecting suitable coformers to prepare cocrystals.

Park et al., utilized differential scanning calorimetry (DSC), a thermal screening tool to verify the possibility of cocrystal formation between emodin (EM) with various coformers. Physical mixtures of emodin and various coformers (1:1 equimolar ratio) were prepared by mixing in glass vials for 1 min. Samples showed DSC profiles of exothermic peaks after an endothermic peak. If cocrystallization is not feasible, an endothermic peak equivalent to eutectic melting is detected, followed by separate compound melting peaks [98].

Zhou et al., investigated a cocrystal screening method using HSM. Based on theoretical assumptions, Berry et al., developed a method using HSM to witness cocrystal formation [99]. Succinic acid, a higher melting point compound, and benzamide, a lower melting point compound, formed a definite mixing zone, which may signify a new cocrystal formation. On a glass slide, the API and coformer are heated until they melt and are covered with a coverslip. After cooling, the mixture is examined under HSM to observe whether cocrystals are formed. In the case of cocrystallization, a mixing zone will appear, where the novel cocrystal phase would be evident and distinguishable from the pure components [100].

Combining the findings of DSC and HSM, these techniques may improve the effectiveness of thermal screening [101].

4. Methods for Preparing Cocrystals

Solution crystallization and solid-state crystallization are the two main types of cocrystal preparation techniques. The preparation of pharmaceutical cocrystals has been discussed by Sheetal et al. [34], and Dennis et al. [94], they further discussed in detail their different possible techniques for the preparation of efficient cocrystals.

The techniques for cocrystal preparation can be generally categorized as green synthesis techniques (also called non-solvent based), solvent-based, and supercritical fluid approaches [102]. Figure 6 includes a list of some conventional cocrystal preparation methods.

4.1. Green Synthesis Techniques or Non-Solvent Techniques

Non-solvent is also a green technique since these techniques require less or no solvent for the formation of cocrystals. They are divided into four types: LAG, extrusion, simple/neat grinding, and hot-melt extrusion [103].

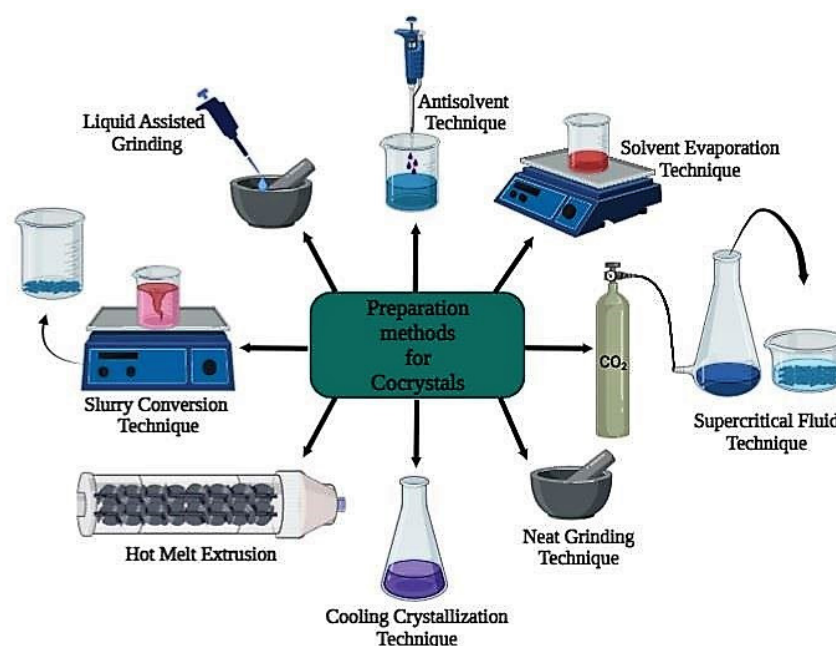


Figure 6. Conventional approaches for preparing pharmaceutical cocrystals.

The neat grinding technique involves mixing two or multiple coformers in a predetermined stoichiometry and grinding them either physically or mechanically for a certain amount of time [104].

The LAG method follows a similar approach as in neat grinding, with the exception that only a small quantity of organic solvent is used during the grinding process [105].

The extrusion process along with a single screw or twin screw helps in mixing coformers with API and is operated below the melting point of the starting material [106].

Hot-melt extrusion, on the other hand, is a specialized process that involves melting and combining coformers simultaneously through a hot screw extruder. Extrusion provides intense mixing, shear, and compact material packing (avoids the use of any solvent) that increases surface contact with coformer blends, resulting in cocrystal formation [107].

4.2. Solvent-Based Techniques

For preparing cocrystals, a range of solution-based processes is known, including evaporative, spray drying, solvent evaporation, slurry, and reactive cocrystallization [93]. A solution- or evaporative-based cocrystallization technique utilizes solvent as a medium that uses undersaturated solutions of both coformer and API [108]. This approach is well-known for producing single crystal cocrystals for diffraction research and crystal structure elucidation.

Cocrystallization via assisted evaporation is comparable to the solvent evaporation technique, where evaporation takes place at higher temperatures and/or at lower pressure [109].

The spray drying process is commonly employed to make ASDs, however new research has shown that it may also be utilized to prepare cocrystals. It is advantageous since the process is continuous, highly controlled, and rapid. Spray drying is a single-step process for converting liquids such as solutions, suspensions, or slurries to solid particles by dispersing an unsaturated liquid of both drug and coformers via a nozzle using nitrogen, where the solvent is quickly removed [110].

The slurry conversion technique (also known as isothermal slurry conversion) entails introducing solid coformers in a predetermined stoichiometric ratio to a solvent (or a solvent combination) for equilibration. This process does not involve a clear starting solution, unlike evaporative cocrystallization. Reactive cocrystallization involves mixing of

coformer and API individually and later adding into either of the clear solutions. Under ambient circumstances, this causes a quick spontaneous cocrystallization [111].

In the ultrasound-assisted solution approach, suitable coformers and API are dissolved in a solvent to produce nanocrystal formulations. To avoid fragmentation and deterioration, the solution is placed in a sonicator and maintained at a constant temperature. The solution is maintained overnight to allow evaporation of the solvent and the development of cocrystals [65].

4.3. Supercritical Fluid Approach

The supercritical fluid technique involves heating a mixture of API and co-former to a temperature close to the melting point of one component (in this case, the co-former) and sustaining these conditions long enough until a single crystal from the multicomponent system is obtained. Unlike organic solvents, supercritical fluid allows relatively faster kinetics and helps in easily removing the organic solvents from the products. This technique also reduces the volume of equipment and expenses of subsequent solvent separation processes during the manufacturing of cocrystals [112].

Cocrystallization through the supercritical solvent approach requires the slurry form of both API and coformer suspended in supercritical CO₂. This method utilizes only the supercritical CO₂ rather than any hazardous organic solvents. Firstly, CO₂ thermodynamics are tweaked to stabilize the density and solvent power. As a result, controlling the cocrystallization process between the cocrystal components shall be possible. The use of this approach resulted in a higher rate of cocrystallization. This is caused by a large amount of mass transfer via convection, which is aided by mixing cocrystal components in a CO₂ slurry, resulting in entire cocrystallization and also a pure cocrystal [113].

The Rapid Expansion of Supercritical Solvents (RESS) technique involves saturating the supercritical fluid (supercritical CO₂) with an API and a co-former before depressurizing the CO₂ phase through a nozzle into a drying chamber with atmospheric pressure. Unfortunately, this technique demands API and co-former solubility in supercritical CO₂, which most pharmaceutical compounds fail to have [114].

The Supercritical Antisolvent Cocrystallization (SAC) process utilizes supercritical CO₂ as an antisolvent. In contrast to RESS, this technique requires less soluble API and coformer throughout supercritical CO₂ in order to precipitate out the two molecules as one. Once the components are added to the vessel, CO₂ dissolves in the solvent, causing a concurrent expansion of the volume and lowering the solvent's solubility, leading to precipitation [115].

Batch gas antisolvent (BGAS) is a process in which a solution containing both API and coformer is saturated in a vessel with carbon dioxide elevated with pressure until cocrystallization completes. Another method is a semi-continuous supercritical antisolvent (SSAS) technique, in which an API-coformer solution is pumped through a nozzle into a highly pressured vessel containing supercritical CO₂ [30].

5. Characterization of Cocrystals

Specific to cocrystal analysis, microscopic, spectroscopic, and thermal methods are widely utilized. To assess developability into a marketable dosage form, physicochemical parameters such as crystallinity, melting temperature, stability, dissolution, and solubility are examined in the same way as any other solid form [116]. The “melting point is a fundamental physical property, which is a thermodynamic process determined by the temperature of equilibrium between the solid and liquid phase when the free energy of transition is equal to zero” [117]. Differential scanning calorimetry (DSC) is a quick way to acquire a melting point and thermal data such as melting enthalpy [118]. Differential Thermal Analysis (DTA) and Thermogravimetry (TG), in addition to the DSC, have been used to determine various factors such as polymorphisms, glass transitions, hydration, decomposition, and stability. PXRD and SCXRD (powder X-ray diffraction and single-crystal X-ray diffraction, respectively) offer structural information, crystallinity degree, and crystal

size [119]. SCXRD has always seemed to be the gold standard, providing complete 3D structural information as well as validating composition, packing, and hydrogen bond configurations [120]. Other spectrophotometric methods, such as infrared (IR), Raman, and nuclear magnetic resonance (NMR), provide extra information that can be used to investigate noncovalent interactions such as hydrogen bonds and associated supramolecular synthons, as well as reflect differences in intermolecular interactions among several crystal structures [121].

Surface topography, particle size, and optical characteristics may all be studied using scanning electron microscopy (SEM) and optical microscopy [122]. Hot-stage microscopy (HSM) integrates microscopy and thermal analysis to offer solid-state characterization as a tool for temperature, allowing for the detection of localized thermal non-uniformity on the sample surface that is overlooked by DSC but visible in HSM pictures [123]. When it comes to orally administered dosage forms, however, stability in both the solid and liquid states is critical. Thermal and relative humidity stress (RHS) was used to evaluate possible solid-state alterations. Thermal methods and PXRD are widely employed in conjunction with high-performance liquid chromatography (HPLC) for degradation testing [124].

Although the characterization techniques for several oral dosage forms serve to be similar to that of the cocrystals, this makes it difficult to differentiate between the salt and a cocrystal. The proton transfer can be in principle estimated by solid-state NMR and/or IR spectra. However, the interpretation of the results in a particular system may be tricky. Still, the SCXRD is an ultimate method for salt/cocrystal determination, while the others are indirect and are easy to misinterpret.

6. Anti-Cancer Drug Cocrystals

Teva Pharmaceuticals recently created a cocrystal of anticancer drug ibrutinib with fumaric acid, which is prescribed for chronic lymphocytic leukaemia. They demonstrated that it has similar solubility to the original medication but is more stable. There is plenty of room for numerous additional cocrystals to develop a pathway. Many researchers have designed several numbers of cocrystals to date to enhance the physicochemical parameters of several anticancer drugs and succeeded in designing the same. Several cocrystals of anticancer drugs are reported in Table 1. Due to their pKa similarities, carboxylic acids, polyphenols, carboxyl amides, and amides are frequently found as co-formers in anticancer drug cocrystals. Most anticancer drugs are either weakly acidic or weakly basic and a few anticancer drugs such as paclitaxel are zwitterionic, too [125].

A pKa range between 0 to 3 of drug and coformer aids in the formation of cocrystals, as stated in the pKa rule of three. da Silva et al. prepared cocrystals of 5-Fluorocytosine based on the ΔpK_a rule and achieved several cocrystals with adipic acid, benzoic acid, succinic acid, terephthalic acid, and malic acid [126].

Nicotinamide and its derivatives are the most commonly used co-formers with anticancer drugs. Since both the amide and pyridine groups are present in the compounds, they can interact as primary synthons.

Hongyan et al. worked on resveratrol cocrystals with nicotinamide and isonicotinamide as coformers and found a huge difference in the drug release patterns and crystal patterns, though the only difference in both the coformers is the placement of the nitrogen atom in the pyridine ring. The only justification for this can be the difference in the gas phase and synthon binding energies between both cocrystals formed [127].

Chenxin et al., investigated two different coformers of palbociclib with resorcinol and orcinol. Cocrystals of palbociclib–resorcinol displayed a better powder dissolution than that of the pure palbociclib. Cocrystals of palbociclib not only improved the dissolution of the drug but also improved the bioavailability which was the greatest drawback of Palbociclib [128].

Adam et al., synthesized cocrystals of quercetin an antineoplastic drug with several co-formers such as caffeine, isonicotinamide, and theobromine. From the obtained dissolution profiles, they proved that cocrystals of quercetin–caffeine had improved the solubility up

to 14-fold when compared to that of pure quercetin. They also performed kinetic studies which proved the improved absorption of the drug through cocrystal technique rather than pure drug where the area under the curve (AUC) was almost 10-fold greater than with the pure quercetin [129].

Urooj et al. prepared cocrystals of nandrolone with salicylic acid by using a grinding technique. They have evaluated the anticancer activity of the cocrystals and the pure drug against HeLa cell lines. The results obtained from the cell line studies proved that cocrystals of nandrolone–salicylic acid. Researchers also found the cocrystals had a synergistic effect and the cocrystals were found to be a potent anticancer agent with anticancer activity comparable to the standard drugs [130].

Yue-Ming et al. utilized the advantages of cocrystals and prepared a recombinant strategy with cocrystallization and nano micelle formation of 5-Fluorouracil with L-Proline as a coformer. The investigators proved that the solubility of the cocrystals was much higher i.e., up to 4.60-fold, and permeability up to 3.89-fold when compared to the pure drug. Eventually, cocrystals also provided excellent anti-tumor activities and restricted their proliferation. Additionally, the prominent slow release of the drug helped in providing a sustained release, which in turn helped to develop a formulation at a lower dose with higher efficacy [131].

Apatinib has a major issue of solubility and hence low oral bioavailability. To overcome this issue Bin et al., reported three innovative cocrystals of apatinib with coformers sebacic acid, adipic acid, and mandelic acid and tried to improve the solubility of the API using the cocrystallization technique. From the studies, they proved that apatinib–sebacic acid cocrystal was successful in increasing the solubility of apatinib up to 7.5-fold. Though solubility has increased to a greater extent, kinetic study results had shown a slight decline in the bioavailability of the apatinib salt form. The stability reports reveal that cocrystals did not convert back to the original apatinib form; this suggests that apatinib–sebacic acid cocrystals have an aqueous stability advantage over the original form [132].

The above-mentioned article proves that alteration of solubility is not just a single parameter that contributes to the bioavailability enhancement of cocrystals. Despite the fact that solubility is a limiting factor in drug oral bioavailability, it is clear that it is not the sole determinant. It is probable that altered metabolism has a significant impact on oral bioavailability.

In general terms, most of the researchers worked on multiple anticancer drugs for enhancing their solubility and stability using various cocrystallization techniques.

Yueming et al., worked on BCS class III drug tegafur to enhance the permeability and its antitumor activity. Researchers have used syringic acid as a coformer to prepare the tegafur cocrystals. The present tegafur–syringic acid cocrystals synchronously enhanced both solubility and permeability. The in vivo pharmacokinetic studies reported a prolonged half-life and enhanced bioavailability when compared to the pure drug. Tegafur–syringic cocrystals were tested on the tumor cells along with the pure drug and displayed a synergistic anti-tumor effect [133].

Meiqi Li and colleagues worked on emodin, a natural dye with various pharmacological activities, such as anticancer, antioxidative activities, anti-inflammatory, and cathartic. Emodin color was changed from yellow to brighter red through cocrystallization using mainly nicotinamide (a colorless coformer) and improving its optical properties [134].

Occasionally, cocrystallization of a drug may not constantly result in solubility enhancement, but instead, it could increase the dissolution rate. Faster dissolution of cocrystals reduces the time to absorb drug from the gastrointestinal tract (decreased T_{max}) followed by phase transformation to a less soluble form.

Shiraki et al. prepared exemestane cocrystals with coformer maleic acid and achieved excellent solubility enhancement and faster dissolution. Though solubility was improved, faster dissolution led to transformation into the unstable crystalline form [135].

Drug–Drug Cocrystals

“Drug–drug cocrystals are composed of two or more APIs established into a new class of solid forms of APIs”. Drug–drug cocrystals are the recent trending approach and are attracting more attention due to their low-cost experimentation and low risk and enhance the physicochemical and biopharmaceutical properties of both the drugs [136]. In order to address the rising need for more effective combination medications such as drug–drug cocrystals, conserving the individual physicochemical characteristics of an API is crucial in such multidrug treatments [137].

Xuan et al. successfully achieved an extended release by preparing drug–drug cocrystals of isoniazid with curcumin, which proved that cocrystals can stand as a promising strategy for achieving an extended release without the use of any polymers [138]. Drug–drug cocrystals not only enhance the properties of any of the drugs present but also are a synergistic pathway during the treatment cycle. When compared to the other dual drug therapy, drug–drug cocrystals may enhance physicochemical attributes such as dissolution, bioavailability, improved solid-state stability, half-life, etc. Even after having several benefits such as dual drug therapy, drug–drug cocrystals have been very rarely designed in the pharmaceutical field due to their own disadvantages. Wang et al. reviewed the future prospects of several drug–drug cocrystals and mentioned multiple factors helping in cocrystal formation. The synthon approach has always been the primary go-to for selecting suitable coformers, but drug–drug cocrystals require a suitable drug with suitable properties such as solubility, compatibility, and less toxicity with minimum adverse effects, which makes selection a quite challenging process. In addition to this, combinations for creating drug–drug cocrystals are also limited since they are mostly reliant on the properties of the drug than the conventional synthon approach [139].

Some of the drug–drug cocrystals available for anticancer drugs during this decade are listed below in Table 2.

Yin and his co-workers worked with lobaplatin and multiple flavonoids and prospered in obtaining the drug–drug cocrystals. Though they couldn’t achieve any enhanced solubility via the cocrystals they were able to crack down the stability issues of the parent drug by decreasing the hydrolysis effect on the parent molecule. On the other hand, some cocrystals failed to improve the solubility of the molecules, rather, they provided sustained release rates which helped to achieve added antitumor activity [140].

da Silva and her co-workers worked on 5-Fluorocytosine with 5-Fluorouracil drug–drug cocrystals. They created drug–drug cocrystals using solvent drop grinding, a green synthesis technique and achieved purely stable cocrystals which are a very important step in cocrystal development [141].

Shridhar et al. cocrystallized gefitinib with furosemide and succeeded in forming cocrystals using solution crystallization. Cocrystal structure study discovered that the components in the crystal lattice are tightly held by strong hydrogen bonds leading to compact crystal packing and enhanced stability. As mentioned, the stronger hydrogen bonds lead to form a more insoluble form of gefitinib than its other stable polymorphs. This increased the retention time of the drug at the place of action [142].

Liu et al. carried out cocrystallization between dihydromyricetin with pentoxifylline and estimated that the solubility of pentoxifylline in an aqueous medium shrinks significantly to 100-fold, while the solubility of dihydromyricetin increases slightly by 1.2-fold. This helps in maintaining a sustained release of both the drugs for up to twelve hours, maintaining the saturation concentration. This drug–drug cocrystal mechanism helped in maintaining a synergetic anticancer effect on the cancer cells [143].

Yin et al. investigated drug–drug cocrystals of oxaliplatin using flavonoids such as baicalein and naringenin and were successful in achieving drug–drug cocrystals with a slow-release rate. Researchers also observed a delayed rate of hydrolysis, which further increases the stability of oxaliplatin. The achieved drug–drug cocrystals of oxaliplatin with baicalein have shown a substantial effect by inhibiting the cancer cells [144].

Jie Wang and his coworkers investigated on a new equimolar drug–drug cocrystal of temozolomide with hesperetin. The formed cocrystals not only improved the stability of the individual drugs but also established an extended dissolution rate which directly helps in the improvement of the physicochemical characteristics of the drug [145].

As listed below, the work on drug–drug cocrystals to date is limited; only four of them were marketed and a few are still in the pipeline for FDA approvals. The development of drug–drug cocrystals has several drawbacks. There is a need for pharmaceutical researchers to develop robust techniques for forecasting drug–drug cocrystals formation. As an outcome, it may fetch a novel prospect for drug–drug cocrystals and new applications to the conventional drug molecules.

Table 1. A list of reported cocrystals of anti-cancer drugs, cocrystal preparation techniques, and its improved parameters from pure API.

Anti-Cancer Drugs	Coformers Used	Preparation Techniques	Enhanced Parameters from Pure Drug	Reference
4,4'-ethylenebipyridine	Flavonoids	Solvent Evaporation method	Improved dissolution behaviour, and anti-tumor activity	[146]
5-Fluorouracil	Ferulic acid	Solvent assisted co-grinding	Improved solubility and permeability	[147]
5-Fluorouracil	Nicotinamide and Iso-Nicotinamide	Solvent-free grinding technique	Improved solubility and stability	[148]
5-Fluorouracil	Proline	Solvent evaporation technique, and Liquid assisted grinding	Improved solubility, permeability	[131]
5-Fluorouracil	Succinic acid, Malic acid Cinnamic acid, and Benzoic acid	Neat grinding and slow solvent evaporation	Improved anticancer activity	[149]
5-Fluorouracil	Urea, Thiourea, Pyrazinamide	Supercritical solvent technique	Improved solubility	[150]
5-Fluorouracil	Urea, Thiourea and Acetanilide	Solid-state grinding method	Improved solubility	[151]
5-Fluorouracil	Gentisic acid, 3,4-Dihydroxybenzoic, 4-Aminopyridine	Solvent-assisted grinding and solution crystallization	Improved permeability and antitumor efficacy	[152]
6-Mercaptopurine monohydrate	2,4-Dihydroxybenzoic acid and Hydroxybenzoic acid	Slurry reactive crystallization	Improved solubility and stability	[153]
6-Mercaptopurine monohydrate	Zinc Tri-fluoro methane sulfonate	Solvent evaporation	Improved solubility and dissolution	[154]
Artemisinin	Acetylene dicarboxylic acid	Green synthesis technique	Improved solubility and dissolution	[155]
Axitinib	Glutaric acid	Solvent evaporation technique	Improved solubility and stability	[156]
Axitinib	Fumaric acid, Cinnamic acid	Liquid assisted grinding and slurry methods	Improved solubility, stability, and oral bioavailability	[157]
Baicalein	Nicotinamide	Slurry method	Improved solubility, dissolution, and bioavailability	[158]
Betulinic acid	Ascorbic acid	Slow solvent evaporation	Improved bioavailability, solubility	[159]
Ceritinib	Nicotinamide, Quercetin	Neat grinding	Improved solubility and stability	[160]

Table 1. Cont.

Anti-Cancer Drugs	Coformers Used	Preparation Techniques	Enhanced Parameters from Pure Drug	Reference
Coumarin	Thiourea	Neat grinding method	Improved antioxidant activity and solubility	[161]
Curcumin	<i>N</i> -acetylcysteine	Anti-Solvent gas Supercritical fluid technique	Improved oral bioavailability	[162]
Curcumin	Ascorbic acid	Solvent evaporation method	Improved solubility, stability, and biological activities	[163]
Curcumin	Trimesic acid	Solid-state grinding, slow cooling crystallization, Evaporative crystallization	Enhanced dissolution	[164]
Curcumin	<i>N</i> -acetylcysteine	Supercritical fluid technology	Improved solubility and dissolution	[165]
Cytarabine	Nicotinamide	Slow solvent evaporation method	Improved solubility	[166]
Dabrafenib	Fumaric acid, Succinic acid and Adipic acid	Solvent drop grinding method	Improved solubility and dissolution	[167]
Dasatinib	<i>N</i> -methyl-4-hydroxybenzoate, Nicotinamide, Ethyl gallate, Methyl gallate, Propyl gallate, Vanillin	Solvent evaporation technique	Improved solubility, stability, and oral bioavailability	[168]
Docetaxel	Nicotinamide	Slow solvent evaporation technique	Improved solubility, dissolution and penetration	[169]
Doxorubicin	Maraviroc	Slow solvent evaporation method	Improved solubility	[166]
Emodin	Nicotinamide	Solvent evaporation	Improved solubility, oral absorption, and bioavailability	[170]
Gefitinib	Isonicotinamide and Vanillin	Solvent evaporation method	Improved intrinsic dissolution, bioavailability, and cell inhibition response	[171]
Ibrutinib	Hydroxy benzoic acid, Succinic acid, Hydroxy naphthoic acid	Slurry method, ultrasonic method	Improved solubility, stability	[65]
Imatinib	Syringic acid	Slurry method	Improved solubility, dissolution, and permeation	[172]
Lapachone	Resorcinol	Mechanical grinding	Improved solubility and oral bioavailability	[173]
Lenalidomide	Urea and 3,5-dihydroxybenzoic acid	Solvent evaporation technique	Improved solubility	[174]
Lenalidomide	Gallic acid	Liquid assisted grinding	Improved solubility, stability, and dissolution	[175]
Lenvatinib	Sulfamerazine	Slow solvent evaporation method	Improved Solubility and stability	[176]
Lenvatinib	Salicylic acid	Slow solvent evaporation method	Improved Solubility and stability	[176]
Lenvatinib	Sulfamerazine and salicylic acid	Slurry reactive crystallization	Improved solubility, stability, and dissolution	[176]

Table 1. Cont.

Anti-Cancer Drugs	Coformers Used	Preparation Techniques	Enhanced Parameters from Pure Drug	Reference
Luteolin	Caffeine	Liquid assisted grinding and rapid solvent removal method	Improved solubility, thermal stability, and bioavailability	[177]
Megestrol acetate	Saccharin	Slow solvent evaporation technique	Improved dissolution	[178]
Nandrolone	Salicylic acid	Grinding method	Improved Anticancer activity	[130]
Nandrolone	3-amino-1,2,4-triazole	Solution reflux method	Improved Anticancer activity	[130]
Palbociclib	Resorcinol	Solvent evaporation technique	Improved solubility, bioavailability, and biosafety	[128]
Palbociclib	Orcinol	Solvent evaporation technique	Improved solubility and dissolution	[128]
Pterostilbene	Picolinic acid	Liquid assisted grinding	Improved oral bioavailability	[179]
Regorafenib	Malonic acid, Glutaric acid and Pimelic acid	Liquid assisted grinding	Improved solubility and dissolution	[180]
Resveratrol	Nicotinamide	Supercritical CO ₂ by the gas antisolvent (GAS) technique	Improved dissolution and bioavailability	[181]
Tegafur	Syringic acid	Liquid assisted grinding and solvent evaporation	Prolonged half-life and increased bioavailability	[133]
Temozolomide	Succinic acid, Oxalic acid	Solvent evaporation technique	Improved solid-state stability, bioavailability, dissolution	[182]
Zoledronic acid	Tartaric acid and Nicotinamide	Slurry method, solvent evaporation, and dry grinding	Improved solubility	[183]

Table 2. Drug–drug cocrystals of anti-cancer drugs reported in the last decade.

Drug Combinations	Therapeutic Category	Preparation Methods	Observations	Reference
Dihydromyricetin with Pentoxifylline	Anticancer and Anti ischemic	Slurry method	Improved solubility and synergistic anticancer effect	[143]
Lobaplatin with Quercetin, Myricetin, Fisetin, Naringenin, and Luteolin	Anticancer and Flavonoids	Slow solvent evaporation method	Improved dissolution, stability, and antitumor effect	[140]
Oxaliplatin with Baicalein	Anticancer and Flavonoids	Solvent evaporation method	Reduced release rate	[144]
Oxaliplatin with Naringenin	Anticancer and Flavonoids	Solvent evaporation method	Delayed hydrolysis	[144]
Temozolomide with Hesperetin	Anticancer and Flavonoids	Liquid assisted grinding	Improved stability and extended dissolution	[145]
Theophylline with Quercetin	Anticancer drugs	Liquid assisted grinding	Improved thermal properties, stability, solubility, and anticancer effect	[184]
5-fluorouracil with Sorafenib	Anticancer drugs	Slurry method	Improved solubility, stability, and antitumor effect	[185]
5-fluorouracil with Regorafenib	Anticancer drugs	Hetero seeding method	Improved solubility, stability, and antitumor effect	[185]

Table 2. Cont.

Drug Combinations	Therapeutic Category	Preparation Methods	Observations	Reference
Propylthiouracil with kaempferol	Anti-thyroid and Anticancer drugs	Solvent evaporation	Improved bioavailability	[186]
Erlotinib with Furosemide	Anticancer and Diuretic drugs	Liquid assisted grinding	Improved solubility, thermal stability, and dissolution	[187]
Gefitinib with Mefenamic	Anticancer and NSAIDs	Liquid assisted grinding	Improved solubility	[187]
Oxaliplatin with Baicalein	Anticancer and Flavonoids	Solution crystallization and liquid assisted grinding	Improved physicochemical properties	[144]
Oxaliplatin with Naringenin	Anticancer and Flavonoids	Solution crystallization	Improved physicochemical properties	[144]
5-fluorouracil with kaempferol	Anticancer and Flavonoids	Slurry method	Improved stability and dissolution	[188]
Berberine chloride with Myricetin and Dihydromyricetin	Anticancer and Flavonoids	Green synthesis	Enhanced solubility and synergistic anticancer effect	[136]
Luteolin with Isoniazid	Anticancer and Antituberculosis	Liquid assisted grinding and rapid solvent removal method	Improved solubility, thermal stability, and bioavailability	[177]
Doxorubicin HCl with Quercetin hydrate and Naringin	Anticancer and Flavonoids	Slow solvent evaporation technique	Improved solubility	[189]
5-Fluorouracil with Aspirin	Anticancer and NSAIDs	Solid-state grinding method	Improved solubility	[151]
Emodin with Berberine Chloride	Anticancer drugs	Slurry method	Improved sustained-release hence absorption	[190]
Imatinib mesylate with 5-fluorouracil	Anticancer drugs	Solvent evaporation technique	Improved solubility and stability	[191]
Dacarbazine with Quercetin	Anticancer drugs	Solvent drop grinding	Improved solubility and dissolution	[192]
Temozolomide with Hesperitin	Anticancer and Flavonoids	Liquid assisted grinding	Improved solubility, stability, and dissolution	[145]

7. Prospects of Cocrystals in the Future

Anticancer drugs have consistent growth in the market and the rise in cancer incidents year to year increases the demand for these drug molecules. This makes those drugs a suitable aim for cocrystallization and overcoming their solubility issues, as discussed previously. Furthermore, it allows scientists to file patents for updated versions of these APIs.

Even though after having all these practical advantages only a couple of anticancer drug cocrystals may hit the market and a few more are still at the clinical trial stage, ibrutinib–fumaric acid cocrystals, used as an anticancer drug to treat chronic lymphocytic leukaemia, are under the process of FDA approval [193].

In this review, several numbers of anticancer drug cocrystals and drug–drug cocrystals were already addressed but the current market situation is contradictory to their achievements.

In the field of cocrystal synthesis, formulation approaches are always evolving, with several procedures to attain the same goal and the search for more dependable methods that require very little time, solvent, and other resources. Earlier, cocrystals were not much explored due to the absence of current technologies, because of which the concept

of cocrystals was not well understood, resulting in a challenging scale-up procedure. Researchers from the pharmaceutical industries have found some significance in developing technologies for cocrystal preparation. Nowadays in-silico and several virtual methods are being adapted for coformer selection and cocrystal design, which helps in reducing practical time and chemical consumption and bringing out a new standpoint in drug development without modifying the molecules chemically [194]. Drug–drug cocrystals are an innovative technique for overcoming some of the issues that typical fixed-dose combinations have. Ashwini et al. reviewed many such case studies and proved numerous abilities of cocrystals; several attempts of cocrystallization of either two or more APIs have demonstrated substantial benefits by enhancing drug efficacy, synergic effects, and mainly the physicochemical parameters without changing API chemically. This leads us to conclude that there is a lot more to explore and utilize the extended-release capabilities of cocrystals, thus proving that there is still a lot of room for advancement in this discipline, allowing for more control over disease treatment, side effects, and dose load [195].

As reported by Zaworotko et al., pharmaceutical cocrystals can be a torch bearer for several such molecules, which require an eye on their drug release patterns to improve their bioavailability. Cocrystals can lead to a new path for all those APIs impacted with poor physicochemical properties directly restricting the solubility and further their oral bioavailability [37].

Nowadays, versatile formulations are capable in imaging, and theranostics have achieved more limelight and been a research interest for many. Wang et al. developed cocrystals that were capable of imaging using near-IR photothermal cocrystals. These cocrystals were synthesized by molecular self-assembly with two small molecules helpful in photothermal imaging. Photothermal imaging has potential applications in various fields which include photothermal therapy (PTT) photothermal/photoacoustic (PT/PA) imaging, photo-thermal-electric devices, and shape-memory devices which are generally utilized in anticancer therapy [196].

8. Conclusions

The steady progress in the total number of research publications on the subject of pharmaceutical cocrystals, as mentioned earlier, indicates the prominence of cocrystallization in the medical field and also shows the keen interest in the researchers. From this review, it seems to be very clear that pharmaceutical cocrystals still carry the limelight around them for their adaptability without changing the scaffold of the chemical structure. However, there are still certain obstacles to overcome, such as coformer selection, physicochemical characterization, and formulation. Successful cocrystal development may be achieved with appropriate API–coformer identification and formulation design. The current review presented different cocrystal screening techniques, including the green screening techniques, which are more advantageous. Several benefits of cocrystallization and fundamentals have been discussed. Nevertheless, as time has passed and the field has advanced, researchers in this area have established several novel techniques, progressively effortless to facilitate cocrystallization procedures, to conquer their preceding limitations. In summary, this review covered several cocrystals and drug–drug cocrystals of anticancer drugs and how these cocrystals have become more popular as a technique to increase the bioavailability of drugs that are water-insoluble. Additionally, the challenges to be addressed and their prospects have been discussed in detail.

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