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REVIEW ARTICLE

Co-Crystals for Drug Design: A Logical Approach for Modifying Physicochemical Properties of Drugs

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Abstract

Drug design plays a critical role in the pharmaceutical industry, addressing the limitations of many compounds with medicinal properties that cannot serve as an effective active pharmaceutical ingredient. Extensive research has been conducted to overcome this challenge, with co-crystals emerging as a promising solution. In drug design, active pharmaceutical ingredients (APIs) often face challenges such as low solubility, poor mechanical properties, or degradation risks. Since the discovery of co-crystals, their potential applications have expanded significantly. Initially recognised as simple solubility modifiers, recent research emphasises their diverse uses, including flavour masking and the enhancement of mechanical properties. With the commercialisation of co-crystal-based drugs, research has shifted from their potential applications to optimise production methods. This article reviews key production methods, including solvent evaporation and hot-melt extrusion, which enable scalable and ecologically sustainable co-crystal synthesis. Addressing poor physicochemical properties, especially low bioavailability, remains a persistent challenge in pharmaceutical development. Co-crystals present an innovative and efficient solution. An API and a co-former are joined by non-covalent interactions to form co-crystals, which are crystalline solids. These structures maintain the natural pharmacological efficacy of pharmaceuticals while improving their physicochemical characteristics, such as stability and solubility. They provide a systematic and rational approach to improve API properties because their design follows well-established crystal engineering principles. This review emphasises the increasing interest in co-crystals and their importance in crystal preparation methods. Co-crystallisation has improved the stability, dissolution rate and solubility of active pharmaceutical ingredients. Although, there are challenges related to scalability, innovative solutions are necessary to ensure consistent and cost-effective production. With ongoing research and advancements in scalable manufacturing, co-crystals are poised to revolutionise pharmaceutical development by overcoming bioavailability challenges and enhancing therapeutic outcomes.

Key words: Co-crystals; Co-former; Pharmaceutical preparations; Biological availability; Solubility; Enhancement; Bulk drugs.

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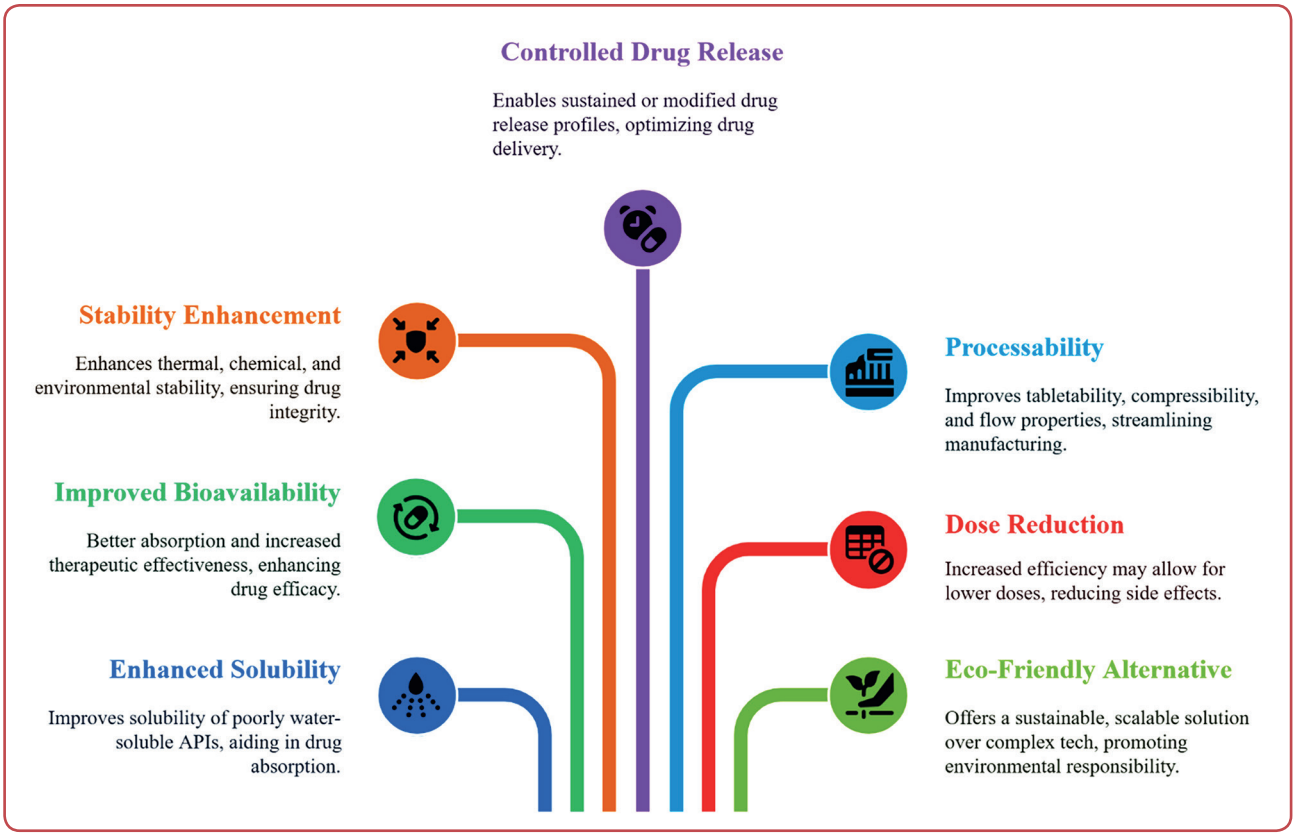

Graphical abstract

Introduction

Drug design aims to develop pharmaceutical compounds with optimal efficacy, safety and stability, but many promising drug candidates fail due to poor solubility, low bioavailability and inadequate mechanical properties. To solve these problems, traditional approaches like salt creation, prodrug generation and nanotechnology have been widely employed; nevertheless, they frequently come with problems with stability, scalability and regulatory approval.

Co-crystals offer a sensible and adaptable substitute for improving the solubility, stability and bioavailability of active pharmaceutical ingredients (APIs) while preserving their inherent pharmacological activity without requiring chemical modification, co-crystallisation provides a calculated method to get around formulation issues by taking advantage of the non-covalent interactions between the API and a co-former. Through non-covalent interactions, such as hydrogen bonds or van der Waals forces, co-crystals enhance solubility, dissolution rate, stability and mechanical strength, leading to better drug absorption and therapeutic performance. Additionally, co-crystals allow for precise control over API properties, enabling the development of tailored drug formulations with improved manufacturability and patient compliance. This makes co-crystallisation a powerful tool in modern drug design, bridging the gap between molecular optimisation and practical formulation challenges. They have revolutionised the pharmaceutical landscape by allowing precise control over the physical characteristics of solid-state drug formulations.[1]

Pharmaceutical co-crystals are crystalline solids made up of several solid components, usually an API and a non-toxic co-former that has been approved for human use. To improve the stability, rate of dissolution and solubility of different APIs, the co-crystallisation approach has been used extensively. Co-crystals have broadened the solid-form landscape of APIs as a unique type of multi-component crystals, offering a methodical

way to maximise their physicochemical characteristics. With growing industry demands, the focus has now shifted towards developing innovative, scalable and environmentally sustainable technologies to improve efficiency and minimise environmental impact.[2]

Historical perspective and definition

In 1844, Wöhler made the first co-crystal discovery when he observed that benzoquinone and hydroquinone combined to form a crystalline compound that was subsequently named quinhydrone. In the past, co-crystals were referred to by a number of names, including addition compounds, heteromolecular complexes and molecular compounds. Lawton and Lopez developed the term "co-crystal" in 1963 and described them as solid crystalline complexes made of bisphenol and organic amines in a patent. But Etter, whose pioneering studies of hydrogen bonding in organic crystals laid the groundwork for the basic ideas of crystal engineering, is largely responsible for the current method of co-crystal design. Two fundamental ideas in the development of co-crystals are:

- Hydrogen bonds are formed by all appropriate proton acceptors and donors.
- Remaining proton donors and acceptors form intermolecular hydrogen bonds after establishing intramolecular hydrogen bonds.[3]

Co-crystals are described as "multi-component, solid, crystalline, supramolecular complexes composed of two or more components within the same crystal lattice wherein the components are in a neutral state and interact via non-ionic interactions" by the Food and Drug Administration (FDA).[4]

- Molecular co-crystals and ionic co-crystals are the two main groups into which co-crystals can be broadly divided.
- Molecular co-crystals are made up of two or more neutral molecules joined by halogen or hydrogen bonds, among other non-covalent interactions.
- Ionic co-crystals contain at least one ionic component and are stabilised by charge-assisted hydrogen bonds or coordination bonds, often involving metal cations.[5]

Co-crystals offer a novel and practical way to alter the physicochemical characteristics of APIs without sacrificing the effectiveness of their treatment. This unique advantage makes co-crystals a more accessible and versatile option compared to other techniques, such as solid dispersion, micronisation, nanoparticle formation, salt formation and similar approaches.[6] Co-crystals are not the same as other solid forms like solvates and hydrates. A solvate has an organic solvent molecule in its structure, whereas a hydrate has a water molecule. Furthermore, co-crystals can also combine with hydrates or salts under certain conditions (Figure 1).[7, 8]

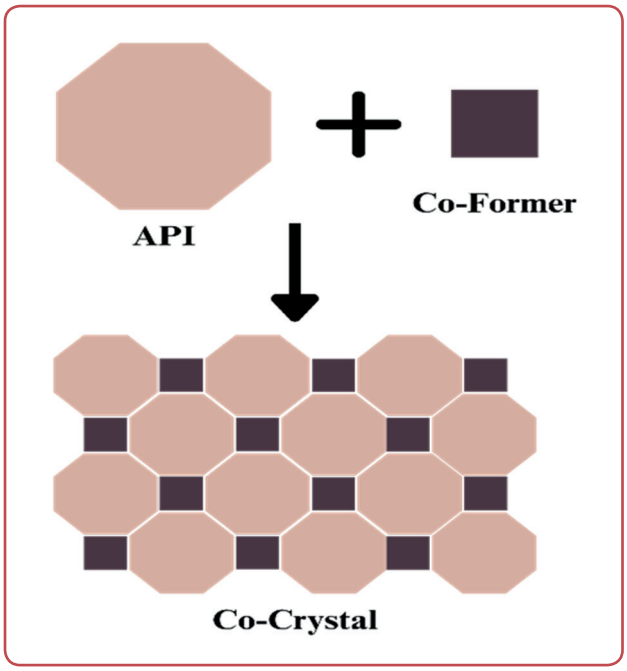

Figure 1: Formation of co-crystals

In order to construct a supramolecular synthon, the API is usually combined with a suitable co-former to form a co-crystal. Zaworotko and Almarsson observed that specific functional groups (or molecular recognition points) within API molecules interact with the co-former, leading to the formation of supramolecular units known as supramolecular synthons.[9, 10] Corey introduced the term "synthon" in 1967 to describe structural components observed in supermolecules that can be created or assembled using known or hypothetical synthetic processes involving intermolecular interactions.[5, 11] There are two types of supramolecular synthons: hetero-synthons, which involve different functional groups and homo-synthons, which have identical functional groups. Through non-covalent interactions, these synthons are essential for maintaining the co-crystal structure. A drug-drug co-crystal

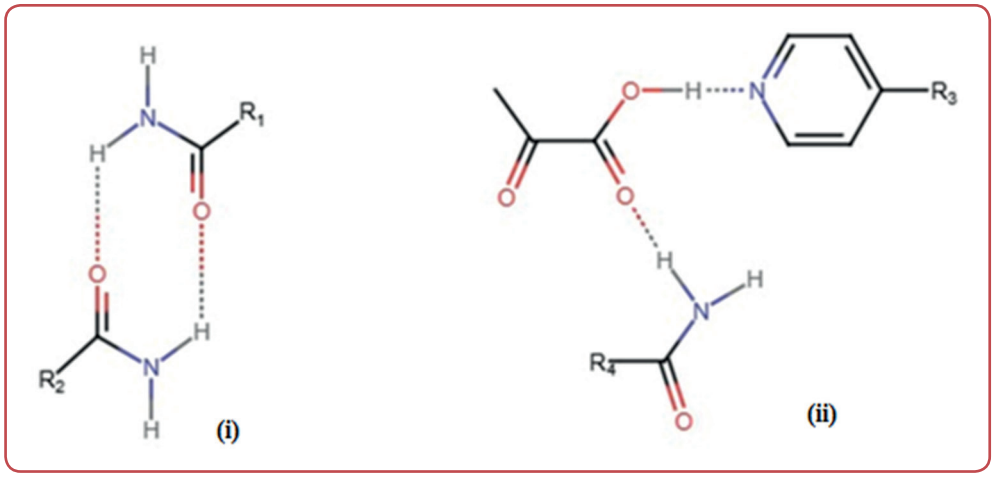

Figure 2: Types of supramolecular synthon; (i) homo-synthon and (ii) hetero-synthon

(DDC) is a co-crystal that is created by combining different APIs. This approach offers a promising way to enhance therapeutic outcomes by optimising the physicochemical properties and delivery of multiple drugs simultaneously.[12] The ΔpKa value can be used to assess the possibility that an API and a co-former will form a co-crystal. A negative ΔpKa (ΔpKa < 0) indicates that no proton transfer occurs between the components, which suggest the potential for co-crystal formation. This rule of thumb helps to predict the compatibility of the API and co-former for co-crystallisation. In contrast, full proton transfer is indicated by a ΔpKa greater than 3, which leads to the creation of salt. In cases, where the ΔpKa falls between 0 and 3, partial proton transfer occurs, often referred to as a salt co-crystal system (Figure 2).[13]

The co-crystallisation technique has become a crucial strategy for modifying drug properties while preserving their therapeutic activity, making it an appealing method for optimising drug delivery. This review explores the increasing interest in co-crystals, supported by recent publications and patents. It talks about several manufacturing techniques, the choice of co-formers and their importance in crystal engineering. It also looks at how scalable co-crystal synthesis is, highlighting methods like solvent evaporation, hot-melt extrusion and other production procedures.

Co-formers

Co-formers are safe, non-toxic molecules that engage with an API by non-covalent interactions such as Van Der Waals forces, π-π stacking, or hydrogen bonds to create a co-crystal. They are crucial for maintaining an API's natural pharmacological activity while improving its physical characteristics, such as solubility, stability and bioavailability. Selecting an appropriate co-former is often regarded as the biggest challenge in synthesising co-crystals. These co-formers can be both active pharmaceutical ingredients and excipients; the techniques used to study and confirm their suitability as co-formers are the same, regardless of whether the compound is an API or an excipient.[14] Co-formers play a crucial role in producing and developing various chemical and pharmaceutical products. This is an in-depth exploration of their importance (Figure 3).[15, 16]

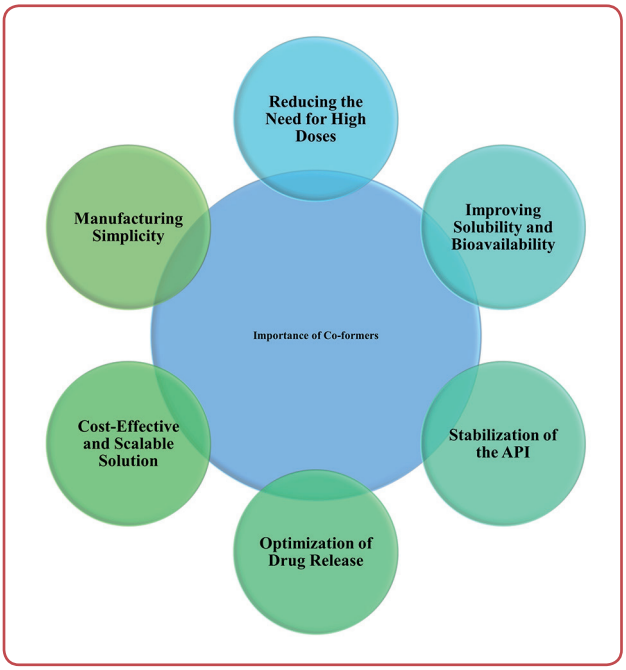

Figure 3: Importance of co-formers
APIs: active pharmaceutical ingredients;

Improving solubility and bioavailability

Drugs in the Biopharmaceutical Classification System Class II and Class III frequently have low bioavailability, which makes absorption extremely difficult. This issue primarily arises from their poor solubility, which prevents the API from dissolving adequately and entering the bloodstream in sufficient amounts to exert its therapeutic effect.[17]

Co-formers significantly enhance the solubility and bioavailability of APIs by forming cocrystals or solid-state modifications, which increase dissolution rates and systemic absorption. This improvement is crucial for achieving better treatment outcomes, particularly for drugs that require high plasma concentrations for therapeutic efficacy.

Stabilisation of the API

A number of environmental variables, including temperature, humidity, oxidation and light exposure, can cause APIs to deteriorate over time. A loss of potency, decreased efficacy, or even safety issues may result from this deterioration.

- Stability enhancement: Co-formers help to protect APIs from environmental stressors by forming stable complexes, reducing susceptibility to oxidation or hydrolysis. This is particularly beneficial for APIs that are sensitive and prone to degradation.
- Polymorph control: Many APIs exist in multiple crystalline forms (polymorphs), each with distinct stability and solubility characteristics. Co-formers aid in stabilising the desired polymorph, ensuring consistent drug performance across different production batches.[18]

Optimisation of drug release

The rate at which a drug is released from its dosage form has a major impact on its therapeutic efficacy (eg tablet, capsule). If a drug is released too slowly or too quickly, it may not achieve optimal therapeutic outcomes.

- Controlled release: Co-formers modify the crystal structure of the API through co-crystallisation, allowing precise control over its release profile. This can enable sustained or controlled-release formulations, ensuring a gradual and prolonged drug release, leading to stable therapeutic levels over time.
- Improved dissolution rates: Co-formers enhance the dissolution rate of APIs, increasing their solubility and bioavailability. This enhances the medication's overall efficacy by facilitating better absorption in the digestive system.

Reducing the need for high doses

High dosages are necessary for many poorly soluble medications to reach therapeutic levels in the body. This may make the production process more difficult and raise the possibility of negative consequences.

- Dose reduction: Co-formers can facilitate the decrease of the necessary dosage by improving the solubility and bioavailability of the API, which will make the medicine safer and simpler to administer. This is particularly beneficial for drugs with a narrow therapeutic window, where the difference between an effective dose and a toxic dose is minimal.[19]

Cost-effective and scalable solution

Other formulation techniques, such as nanotechnology or lipid-based formulations, can be effective but are often costly and may not be scalable for large-scale manufacturing. In contrast, co-formers offer a simple and cost-effective approach to enhance an API's properties.

Simplicity: Unlike complex techniques that require specialised equipment and advanced technologies, the selection and formulation of co-formers are generally a straightforward process, making it a practical and efficient alternative.

Manufacturing simplicity

Co-crystals and co-former-based formulations are generally compatible with conventional pharmaceutical manufacturing processes, allowing for large-scale production without requiring significant modifications to existing infrastructure. This makes them a practical and scalable solution for enhancing drug properties while maintaining cost-efficiency in manufacturing.[20]

Ongoing research and technological advancements are expected to make co-crystals a transformative element in pharmaceutical development. They offer a practical means of improving medication stability, solubility and bioavailability, all of which can contribute to improved ther-

apeutic results. However, challenges still exist in large-scale production, necessitating innovative solutions to ensure cost-effective and sustainable manufacturing.

Examples of co-formers

Co-formers are selected based on their ability to enhance the physicochemical properties of an API. Co-formers, which can form complexes, cocrystals, or salts with APIs, are commonly encountered and include organic acids, bases, amides and salts. Examples of well-known co-formers utilised in the pharmaceutical sector are listed below:[21, 22]

1. Saccharin

Co-former type: Organic acid

Example and application: A common co-former in co-crystals formulations, saccharin helps to make poorly soluble APIs more soluble. When ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), is mixed with saccharin, co-crystals are created, these increases the solubility of the medication and increase its bioavailability (Figure 4).

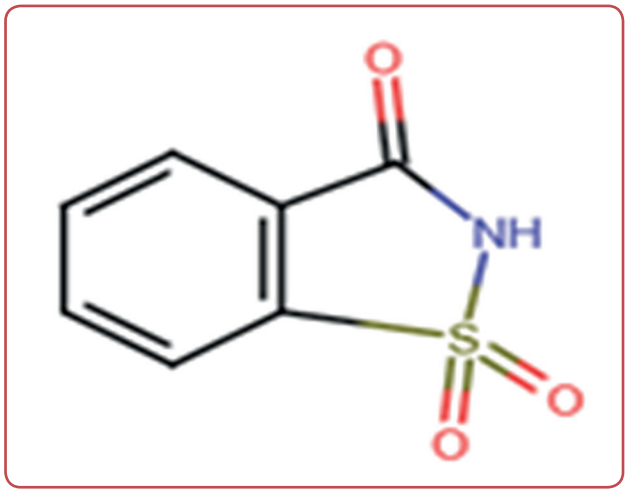

Figure 4: Saccharin

2. Nicotinamide

Co-former type: Vitamin (B3 derivative)

Example and application: Nicotinamide is commonly used as a co-former to improve the solubility of medications that are not very soluble in water, like carbamazepine and ibuprofen. Nicotinamide increases these APIs' bioavailability and dissolution rates by creating co-crystals with them, which increases their efficacy. Additionally, its hydrogen-bonding ability makes it an excellent choice for stabilising various drug formulations, ensuring prolonged shelf life and consistent therapeutic outcomes (Figure 5).

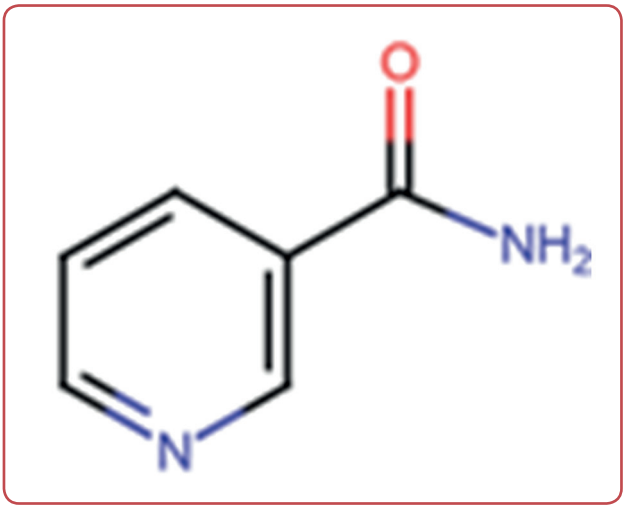

Figure 5: Nicotinamide

3. L-Proline

Co-former and type: Amino acid

Example and application: L-proline, a naturally occurring amino acid, combines with APIs to create stable co-crystals, such as theophylline and caffeine. L-proline as a co-former improves the solubility of drugs, thermal stability and mechanical properties, making it a valuable choice for improving pharmaceutical formulations. Moreover, L-proline-based co-crystals can help to reduce the risk of drug degradation, thereby, extending the drug's efficacy over time (Figure 6).

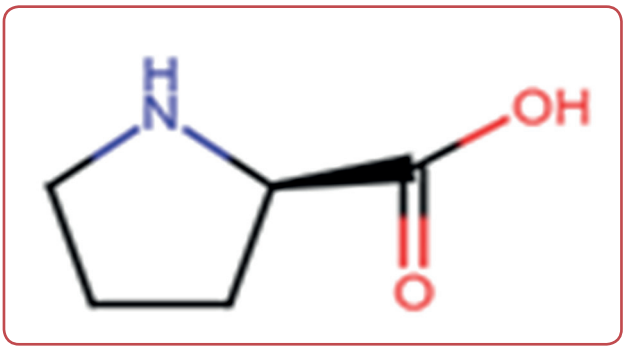

Figure 6: L-proline

4. Picolinic acid

Co-former type: Organic acid

Example and application: Picolinic acid, an organic acid with strong hydrogen-bonding capabilities, has been applied to improve the stability and solubility of APIs such as nicotinamide and caffeine. It is essential for altering drug release patterns, which guarantees a better regulated and prolonged release of pharmaceuticals. Additionally, picolinic acid co-crystals being investigated for their potential to increase the amount of bioavailable certain antibiotics and anticancer drugs.

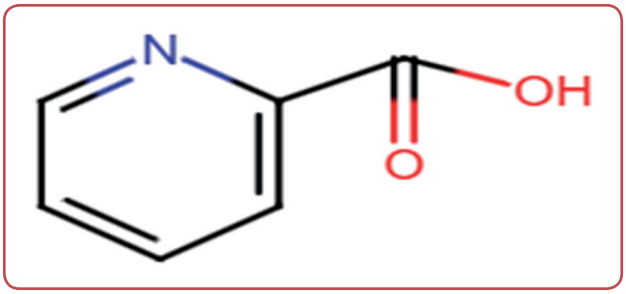

Figure 7: Picolinic acid

Co-formers are substances used in combination with basic ingredients (such as active compounds or other essential components) to enhance the food product's stability, functionality, or texture. This term is used in the context of food science and formulation. They usually improve the performance, texture and qualities of the finished product by combining with other ingredients (Figure 7).[23-25]

Selection of co-formers

Co-formers are essential to the creation of co-crystals. When selecting a suitable co-former, several factors must be considered, including molecular size, functional group type, physical form and pKa.[26] Compounds classified as Generally Recognised as Safe (GRAS) are frequently utilised in the development of multi-component crystals as part of a broader co-former selection strategy (Figure 8).[27]

The selection process relies heavily on understanding the API and experimental approaches. The trial-and-error method is commonly used in experimental studies, with co-crystal identification carried out using analytical techniques such

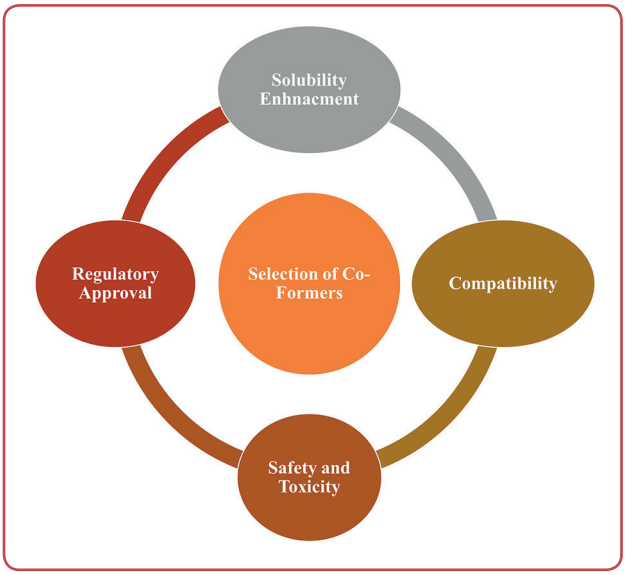

Figure 8: Selection of co-formers

as Raman spectroscopy, Fourier transform infrared spectroscopy, differential scanning calorimetry, powder X-ray diffraction, single crystal X-ray diffraction and others. However, the process of formulating and identifying co-crystals is often time-consuming and resource-intensive. To optimise efficiency, alternative methods can sometimes be employed to bypass the trial-and-error approach. Effective co-former selection can be achieved through pKa-based models, supramolecular synthon compatibility checks, hydrogen-bonding analysis, the Cambridge Structural Database (CSD), thermal analysis calculations, lattice energy calculations and saturation temperature measurements.[28, 29]

Co-former screening and selection techniques

Hypothetical /theoretical method

Hydrogen bonding

The success of co-crystallisation is significantly influenced by the number of hydrogen bond acceptors and donors present in both the drug and co-former molecules.[30] Hydrogen bonding, defined as the interaction between an electronegative atom (X) and a hydrogen atom, existing either within a molecule (intramolecular) or between different molecules (intermolecular).[31] The favoured stereo-electronic properties, selectivity and connectivity patterns of hydrogen bonds linked to particular functional groups or combi-

nations of functional groups involved in hydrogen bond formation are all elucidated by the hydrogen bond rule. Donohue and Etter established the Hydrogen Bond Rules to predict the conditions favourable for hydrogen bond interactions that lead to co-crystal formation (Figure 9).[32, 33]

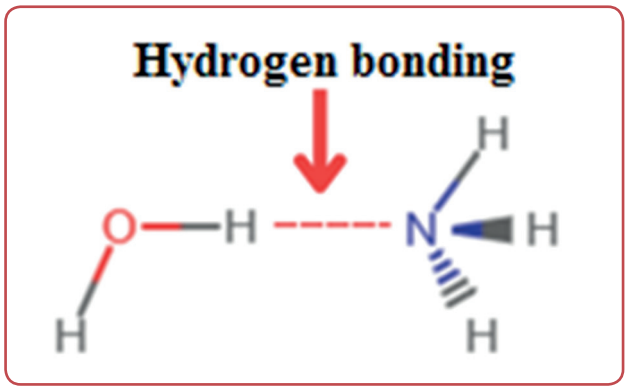

Figure 9: Hydrogen bonding

Some key conditions include:

a. Effective acceptors for protons (eg –OH, $–NH_3$) and donors of protons (eg –COOH, $–NH_4^+$) are frequently a part of hydrogen bonds.

b. Before intermolecular hydrogen bonds (like N-H···O and O-H···O) are established, six-membered ring intramolecular hydrogen bonds (like C-H···O) are formed.

a. The best proton donors and acceptors take part in intermolecular hydrogen bonding once intramolecular hydrogen bonding has occurred.

b. In the crystal structure, hydrogen bonds are formed between all acidic hydrogen atoms.

These guidelines offer a framework for comprehending and forecasting how hydrogen bond interactions result in the development of stable co-crystals.

pKa rule

The ΔpKa value acts as a crucial determinant for evaluating a co-former's suitability in developing a co-crystal with a desired API. pKa, representing the negative logarithm of the dissociation constant, measures an acidic molecule's ability to donate a proton. A negative ΔpKa, indicating no proton transfer between the co-former and API, suggests the potential for co-crystal formation. Its pH-dependent solubility and rate of dissolution allow the BCS Class II medications to be further divided into IIA (acidic drugs), IIB (basic drugs) and IIC (neutral drugs). Conversely, if the ΔpKa value exceeds 3, a salt is likely formed due to complete proton transfer. The range of 0 to 3 is considered a gray area, where accurate predictions are difficult.[3, 9] The equation used to predict co-crystal formation is:

Aghara et al utilised this equation to develop and

$$\Delta pKa = pKa\ (Base) - pKa\ (Acid)$$

design two luliconazole co-crystals with having menthol along with mannitol and achieved a five-fold increase in the solubility of luliconazole compared to the pure drug.[10]

Supramolecular synthon approach/molecular recognition points

Designing co-crystals using hydrogen bonding principles and the molecular recognition points approach involves the following steps:

a. Finding the functional groups that are present in the co-former and API molecules.

b. Assessing the intramolecular interactions between the API's individual drug molecules.

c. Determining possible functional groups that could take part in interactions between molecules inside the pure compounds.

d. Determining the probability that several molecules will interact with one another.

e. Choosing co-formers by assessing the interactions between and among molecules.

There are two types of supramolecular synthon approaches: Hetero synthon and Homo synthons, depending upon the interacting functional groups found in the medication and co-former. When self-complementary functional groups, such amide + amide or acid + acid groups, contact, homo synthons are created. In contrast, hetero synthons arise from the interaction of two different functional groups, such as acid + pyridine, acid + amide, or amide + pyridine groups.[34] This approach provides a systematic framework for designing co-crystals by leveraging specific functional group interactions.

Experimental methods/pick and trial approaches

The experimental approach for co-crystallisation involves conducting studies using small quantities of both the API and co-formers. For the primary purpose of screening possible co-formers, mechanochemical synthesis techniques including solvent-based grinding and neat (simple) grinding are recommended. These techniques rely on kinetic energy to drive the co-crystallisation process.[35]

In this method, the API and co-former are ground together in equimolar ratios for a specific duration using either a ball mill or a mortar and pestle.[36]

In silico techniques

Lattice energy assessment

The degree of ionic bonding in an ionic substance is measured by lattice energy. It describes the energy shift that takes place when one mole of a crystalline ionic compound develops from its constituent ions in the gas phase, or the energy needed to fully dissociate one mole of an ionic compound into its constituent ions in the gas phase. Lattice energy is utilised in virtual screening, which applies thermodynamic principles to predict potential co-formers.[37] A co-crystal phase is typically favoured if it is more thermodynamically stable than the pure components, meaning the lattice energy of the co-crystals should be greater than that of their elements.[38] The lattice energy of a molecule can be calculated using the following formula:

$$\Delta E_{leLE} = \Delta E_{lrLE} + \Psi_{leLE}$$

Where:
ΔE_{leLE} = Lattice energy
ΔE_{leLE}= Conformational intramolecular energy
Ψ_{leLE} = Intermolecular lattice energy

The probability of co-crystallisation rises with a greater difference between the lattice energy of the pure components and that of the co-crystals.[39] Chan et al employed a thermodynamic approach to predict the formation of co-crystals of paracetamol with various co-formers.[40] Neutral molecules, salts, solvates and other solid and liquid systems can all be assessed using the lattice energy assessment method. Notably, this method does not require assumptions about hydrogen bonding.[41]

Cambridge structural database (CSD)

Supramolecular retrosynthetic analysis involves identifying the intermolecular units required to achieve the desired co-crystal structure, utilising the CSD. The CSD, which presently houses more than 1.2 million crystal structures, includes crystallographic information on hydrogen bonds that form between medications and co-formers. With nearly 40,000 new structures added each year, the CSD serves as an efficient and well-designed software tool.[42, 43] It can predict stable hydrogen bond motifs and verify consistency across a range of core structures.[44] Additionally, the CSD provides hydrogen bonding propensity tool, which assists in the design of co-crystals. Each entry in the CSD offers detailed information on chemical structure, crystallographic data, molecular geometry, crystal packing, stereochemistry, molecular dimensions, structure representation and conformational analysis.[45-47]

By leveraging insights into preferred orientations and geometries of current intermolecular interactions, researchers can select co-formers for co-crystallisation with APIs.[48, 49] Analysing statistical datasets of co-crystals available in the CSD empowers researchers to employ virtual screening methodologies to identify viable co-crystal-forming combinations. This approach facilitates the construction of co-crystals through molecular modelling, resulting in significant time and cost savings.[50]

Conductor-like screening model for real solvents (COSMO-RS)

An increasingly popular substitute for high-performance thermodynamic analysis is COSMO-RS. It predicts co-crystal formation by evaluating the differences in residual enthalpies between individual components and the co-crystals, assuming that interactions in the supercooled phase are similar to those in the solid phase. As a high-throughput screening tool, COSMO-RS is particularly valuable for screening hydrates and identifying the most suitable solvent for co-crystallisation.[51, 52]

In a study by Wu et al, COSMO-RS, among other models, was investigated for predicting the co-crystal formation of a host molecule with 63 other molecules. The results demonstrated that COSMO-RS is a potent and reliable method, achieving an overall hit rate of 84.1 %.[53]

Methods of preparation of co-crystals

Various techniques can be employed to prepare co-crystals and these methods are categorised based on the solvent and state of matter involved. There is no single method that guarantees the de-

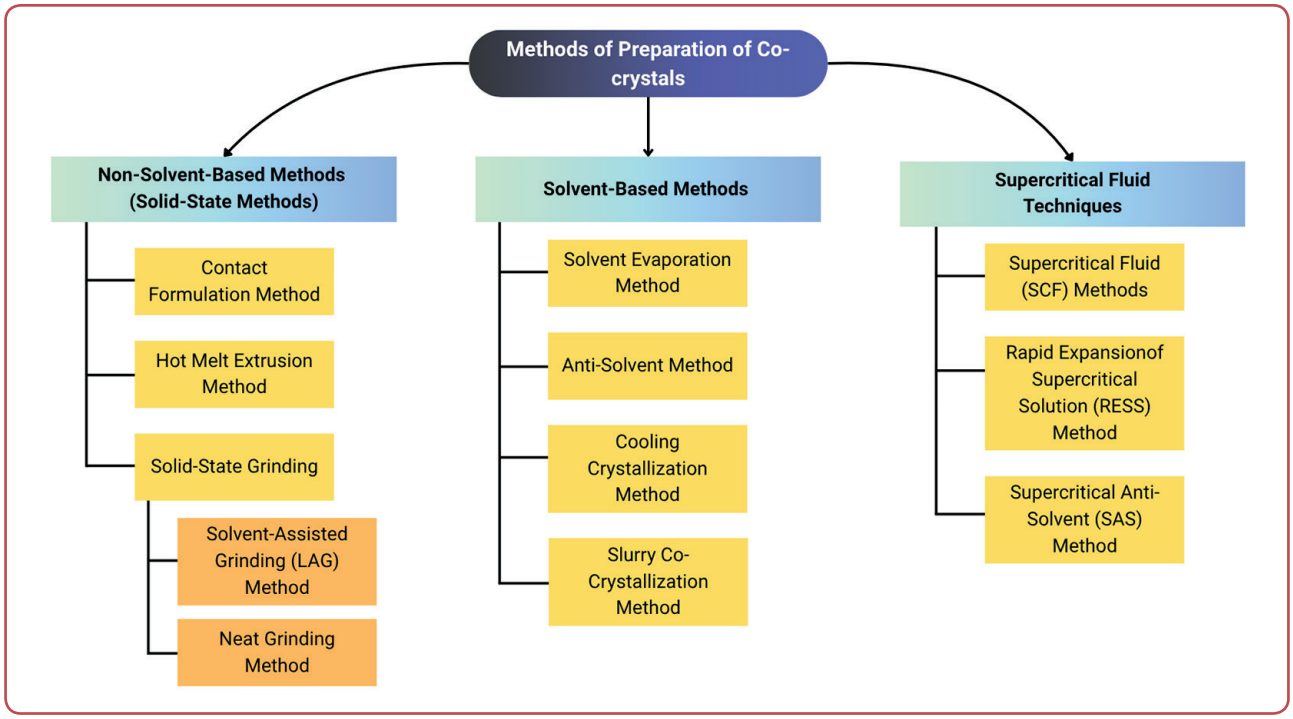

Figure 10: Methods of preparation of co-crystals

sired outcome for co-crystal production. The appropriate method is selected according to the specific properties to be enhanced.[54] The three main categories of preparation methods are supercritical fluid techniques, solvent-based approaches and non-solvent-based procedures. Green synthesis methods focus on environmentally friendly processes, while solvent-based methods involve using solvents to facilitate co-crystal formation. Supercritical fluid approaches utilise supercritical fluids to promote co-crystal formation, offering unique advantages in terms of selectivity and efficiency (Figure 10).[55] Each method presents its own challenges. For example, obtaining co-crystals through mechanochemical methods can be complex. In solution-based techniques, selecting an appropriate solvent for co-crystallisation is a critical challenge and the formation of solvates or hydrates cannot be entirely avoided.[56] Another notable approach for co-crystallisation is the cocktail method, which involves co-grinding the API with more than two co-formers, potentially saving time and cost.[57]

Non-solvent-based methods

Solid-state grinding

Non-solvent based methods provide a sustainable and solid-state approach to co-crystal synthesis, aligning with green principles by minimising or eliminating solvent use. These methods consist of liquid-assisted grinding (LAG), neat grinding, extrusion and hot-melt extrusion. Each method offers distinct advantages in terms of efficiency, scalability and environmental impact, expanding the range of tools available for co-crystal preparation.[21]

Neat grinding method

Either manually or mechanically, the target molecule and co-former are combined in a predetermined stoichiometric ratio and ground for a predetermined amount of time. This process involves applying pressure using a mechanical system (such as a ball mill with an automated setup) or manual tools (like a mortar and pestle).[58, 59] A key limitation of the dry grinding method is its inability to guarantee the formation of a stoichiometrically consistent mixture of co-crystals, often requiring an additional step to achieve a pure co-crystal product.[60]

Solvent-assist grinding method

LAG is a milling technique that adds a small amount of solvent during or before grinding.[61] Research indicates that this method can effectively produce co-crystals, such as those of adefovir dipivoxil and glutaric acid. By using an organic solvent, LAG accelerates the co-crystallisation process compared to traditional grinding meth-

ods, making it a preferred choice due to its higher success rate and widespread application.[62]

Hot melt extrusion method

Extrusion is the process of changing a material's physical properties by forcing it through a die or aperture under controlled conditions. This unique technique combines the simultaneous mixing and melting of the co-former and API using a heated screw extruder. The raw ingredients are usually put into the heated extruder in a molar ratio. Melting takes place, allowing the initial ingredients to be thoroughly mixed. Direct co-crystals nucleation occurs in the melt and continuous isolation of pure co-crystals extrudate from the extruder is achieved.[63] Co-crystals of hydrochlorothiazide have been formed through hot melt extrusion using co-formers like nicotinamide, resorcinol and catechol.[64] Hot melt extrusion single-step strategy has a greater advantage over other ancient strategies.

Contact formulation method

The contact formulation method focuses on enhancing the crystallisation rate of particles while reducing their size. Pre-milled crystals play a crucial role in facilitating the spontaneous reaction that leads to co-crystal development. Many co-crystals have been created using this technique, demonstrating that smaller particles result in faster co-crystallisation. For example, urea and 2-methoxybenzamide exhibit increased surface energy due to their reduced particle size, accelerating the co-crystal formation process.[64]

Solvent-based method

Various solution-based methods are used for co-crystal preparation, including spray drying, evaporation, slurry, reactive co-crystallisation and solvent evaporation.[65] In evaporative or solution-based co-crystallisation, solvents act as the medium, using under saturated solutions of the co-former and the API. This method is particularly noteworthy for generating single-crystal co-crystals, which are valuable for diffraction research and crystal structure elucidation.[66] Moreover, solution-based techniques offer flexibility in controlling factors such as temperature, concentration and solvent choice, which can influence co-crystal formation. For example, spray drying involves atomising a solution into fine droplets and rapidly evaporating the solvent to produce solid particles, while slurry methods involve suspending the drug and co-former in a solvent to promote crystallisation. These diverse approaches provide researchers with tools to tailor co-crystal properties to meet specific formulation and therapeutic needs.[67]

Solvent evaporation method

Various articles described the formation of co-crystals using the solvent evaporation method like co-crystal of quercetin with succinic acid prepared in 1:1 molar proportion by utilising solvent evaporation technique.[68] It is one of the most common methods used for co-crystals preparation, which involves dissolving drug and co-former at a stoichiometry ratio in a particular solvent, stirring the mixture constantly to promote molecular interaction between the two and allowing the solvent to evaporate to form a solid known as co-crystals (Figure 11).[34]

Anti-solvent method

This approach involves treating a solution with an anti-solvent to decrease the solute's solubility, which results in the creation of crystals. For example, the anti-solvent co-crystallisation method is used to create the co-crystals of carbamazepine and saccharin. Methanol, in combination with water, effectively facilitates this process.[69] When water is added to a room-temperature methanol solution of carbamazepine and saccharin, co-crystals nucleate in two to three minutes. After 30 minutes, co-crystallisation is complete, yielding 84.5 % solid on a carbamazepine basis. This method is an efficient alternative to cooling and evaporating co-crystallisation method as it requires less energy and can be conducted at room temperature (Figure 12).[70]

Cooling crystallisation method

Cooling co-crystallisation relies on temperature-dependent solubility changes to produce co-crystals. The temperature of the solution is decreased to obtain supersaturation after dissolving both co-formers and target molecules in a solvent.[71] Using this approach, Kumar et al employed the cooling crystallisation method to prepare a co-crystal of luliconazole, aiming to improve its solubility and dissolution rate.[72]

Slurry co-crystallisation method

A slurry is a mixture of solid particles suspended in a liquid. Slurries can be used to transport large solids, such as soil and are also utilised in various fields, including co-crystals.[73] This is the most

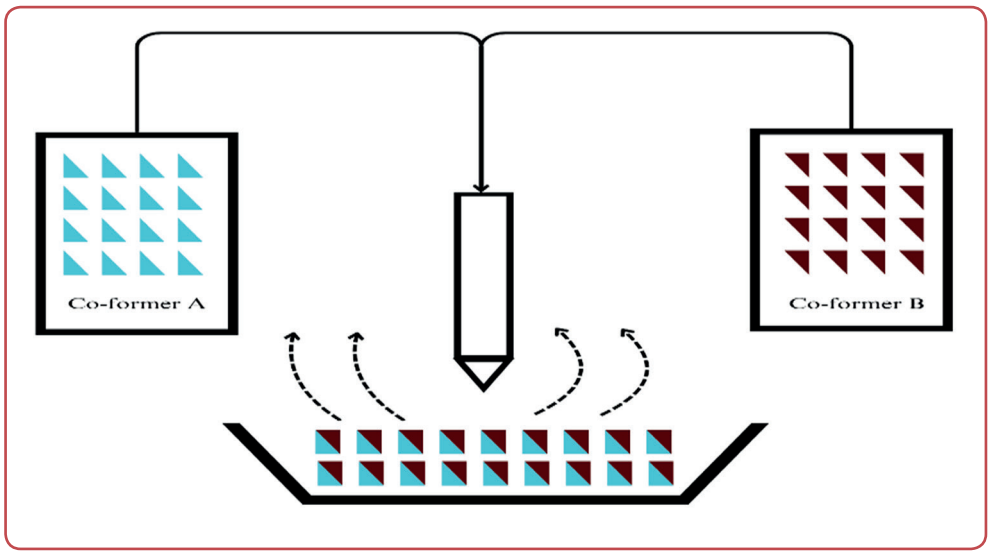

Figure 11: Solvent evaporation method

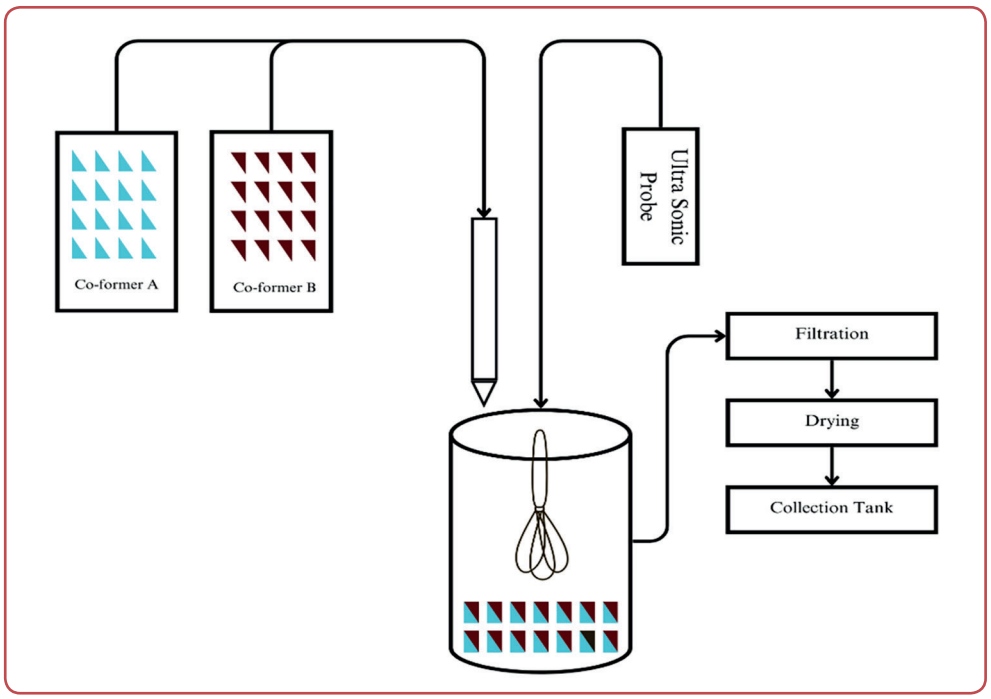

Figure 12: Anti-solvent method

effective screening and scaling-up technique for co-crystallisation.[74] Using this technique, the co-former and API are dissolved in separate solutions at the proper temperature and stirred for the required duration. Then, the constituent concentration is found to be greater than the co-former's critical activity, allowing nucleation growth and crystal formation (Figure 13).[75]

Reaction method

This approach used a solution containing reactants to produce the co-crystals. Crystals occur when a substance is added to another solution and stirred in a vessel because the concentration in the mixture is greater than the solubility. This kind of approach typically involves rapid reactions and the mixing conditions have an impact on the size of the crystals. The expansion of nucleation is dependent on mixing at the microstate level, which results in supersaturation and decreased solubility.[76] Using this approach, by Ma et al meloxicam co-crystals containing acidic co-formers such as maleic acid and salicylic acid were obtained.[77]

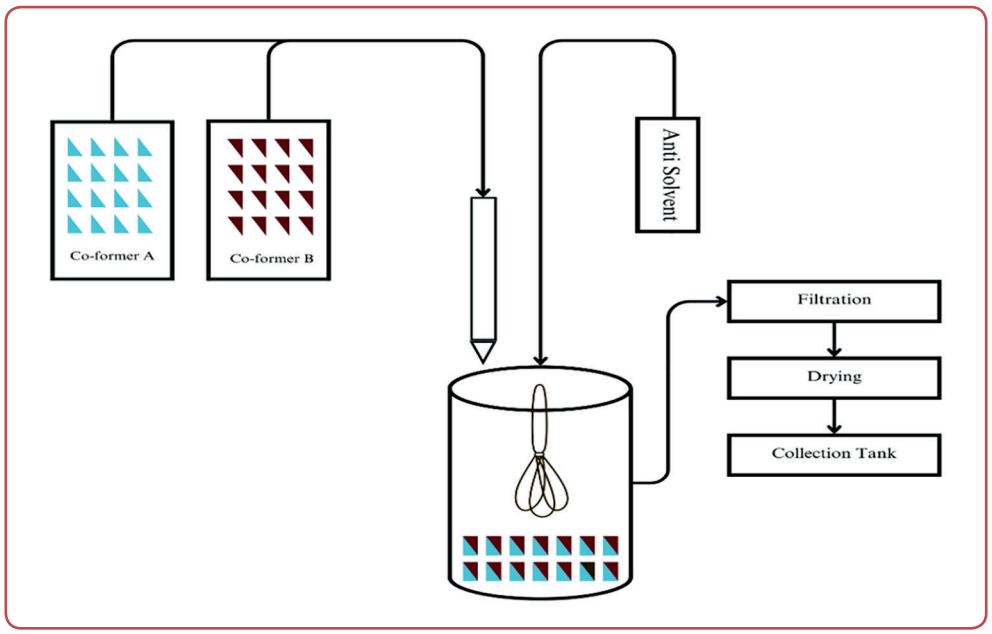

Figure 13: *Slurry co-crystallisation method*

Supercritical fluid techniques

Supercritical fluid (SCF) methods

The SCF method involves a mixing of co-former and API with constant heating to the melting point or a temperature close to the melting point of one component, usually the co-former. In order to create a single crystal from the multicomponent system, these states are maintained. Supercritical fluids allow for the effective removal of organic solvents from the final product, dissimilate to normal organic solvents and offer faster kinetics. Additionally, This approach avoids the need for elaborate solvent separation processes and associated equipment during co-crystal manufacturing, thereby lowering both operational costs and environmental impact. Supercritical fluid technology is gaining prominence in pharmaceutical research and development due to its versatility, efficiency and environmentally friendly attributes. It offers precise control over process parameters, enabling the creation of co-crystals with specific characteristics including polymorphic shape, particle size and morphology. Additionally, the use of supercritical fluids enables the exploration of novel co-crystal systems and enhances the scalability of co-crystal production for commercial applications.[78]

Supercritical solution rapid growth

Solutes that are very soluble in supercritical fluids, such as CO_2, can be dissolved in them. This technique rapidly depressurises the solution by expanding it through a nozzle. This phenomenon was first described in the 1980s and is well-known as the supercritical solutions' quick growth. The solubility of solute in CO_2 is reduced due to the lower density caused by depressurisation. This immediate decrease in solubility leads to a high degree of supersaturation of the solute. As a result, the solute precipitates out of the solution. Rapid expansion of supercritical solution has the advantage of being a mild operating technique that is ecologically benign and produces tiny particles in a single step without leaving behind solvent residues as compared to traditional precipitation processes.[79]

Supercritical anti-solvent method

A solvent that is miscible with SCF is used to distribute the solute or solute + carrier. Solvents that satisfy this requirement include ketones like acetone and dimethyl sulfoxide as well as alcohols like ethanol, methanol and propanol. Subsequently, this solution is added to SCF CO_2, which can be either liquid or gaseous and it functions as an antisolvent to induce supersaturation in the mixture.[19]

SCF CO_2 has been used in two different methods to produce cocrystals. In the first method, a solution is saturated with CO_2 inside a high-pressure vessel until co-crystallisation occurs. This process is known as the batch Gas Antisolvent treatment. The co-former and dissolved API are

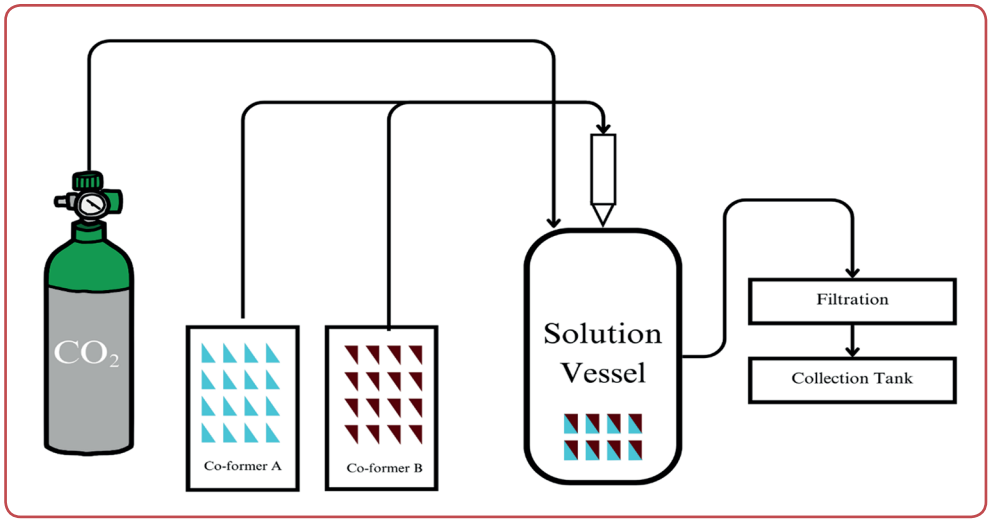

Figure 14: Supercritical anti-solvent method

present in the solution. A solution including the dissolved API and co-former molecules is forced via a nozzle into a high-pressure vessel filled with supercritical CO_2 in the second method, which is called the semi-continuous supercritical antisolvent process (Figure 14). In both methods, CO_2 dissolves in the solvent, which increases its volume and decreases its solubility, leading to precipitation at the end.[80]

Regulatory hurdles in the usage of pharmaceutical co-crystals

Co-crystals are classified differently worldwide: the FDA sees them as new solid drug forms, while the EMA considers them new active substances. Key regulatory points include proving co-formers are pharmacologically inactive to ensure safety and efficacy. Challenges involve demonstrating bioequivalence, stability and consistent manufacturing. Regulatory bodies require dissolution, bioavailability and stability studies. Issues such as stability risks, manufacturing variability and patent uncertainties also exist. Overall, clear, harmonised regulations are needed to facilitate development and commercialisation.

Co-crystals applications

Co-crystals offer stable crystalline shapes without creating or breaking covalent bonds, unlike amorphous solids. They can form from any API molecule, whether ionisable or not. Examples include food additives, preservatives, excipients and APIs. Co-crystals are designed via crystal engineering, making them patentable and advancing intellectual property. They can be manufactured using green, solvent-free processes with high yields. In pharmaceuticals, co-crystals help extend the patent life of active ingredients by resolving IP issues.

Improve stability

The stability of a pharmaceutical product significantly affects its colour, appearance and efficacy. Poor stability can lead to a drug's toxicity, degradation and diminished therapeutic efficacy. Therefore, maintaining the stability of a pharmaceutical product over its shelf life is essential. Co-crystals have been demonstrated to increase API stability. Hygroscopic drugs and excipients are particularly prone to unexpected phase changes and instability issues, which can hinder their effectiveness during several stages of the pharmaceutical process, including production, packaging, storage and transportation. These instability issues can also significantly affect the appearance and performance of the final product.[81]

Enhance solubility

A drug's solubility, which has a direct effect on the drug molecules' bioavailability, is one of the main determinants affecting its therapeutic efficacy. The medicine's solubility determines whether the systemic circulation contains the required concentration of the drug. Co-crystals present a viable way to increase the solubility of medications that are not very soluble in water. Co-crystallisation has been shown in numerous

studies to increase the solubility of such medications. For instance, the solubility of apixaban has significantly improved when it is co-crystallised with the co-former oxalic acid. Apixaban is a medication primarily used to inhibit the blood coagulation factor Xa. It is not very soluble in water. Compared to the marketed product, research shows that the Apixaban co-crystal is more soluble, demonstrating the potential of co-crystals to address solubility issues.[75]

Aghara and Kiran Dudhat had explored the use of cooling crystallisation to develop new solid forms of drug-co-former co-crystal complexes. This method enabled the replication of known co-crystal phases and the creation of novel mixtures, including co-crystals of luliconazole with mannitol and menthol. These co-crystals were studied using analytical techniques like PXRD, thermal methods and FTIR. The results showed a reduced heat of fusion, which suggested enhanced entropy and solubility. In contrast to pure luliconazole, the luliconazole: menthol co-crystal notably showed a five-fold increase in solubility. The study concluded that cooling crystallisation could effectively enhanced the solubility and dissolution of luliconazole by altering its crystal structure.[82]

Improve bioavailability

For example, carbamazepine co-crystals containing co-formers such glutaric acid, succinic acid, adipic acid and malonic acid have shown enhanced solubility and bioavailability of the drug, which was previously thought to have low bioavailability. The bioavailability of carbamazepine co-crystals was substantially higher than that of the pure drug, according to *in vivo* pharmacokinetic experiments conducted on animals. This was especially true when glutaric acid was added as a co-former.[69]

Another study examined baicalein (BE), a flavonoid with significant pharmacological advantages, such as anti-inflammatory and anti-cancer effects, by Pi et al. Its therapeutic potential is, however, limited by its poor oral absorption and poor solubility. The researchers used a nano-co-crystal approach to increase the bioavailability and rate of dissolution of BE. Utilising high-pressure homogenisation, they produced baicalein-nicotinamide (BE-NCT) nano-cocrystals and assessed them *in vitro and in vivo*. In comparison to BE coarse powder, the nano-cocrystals, which have an amorphous form and an average particle size of 251.53 nm, demonstrated a 2.17 to 2.54-fold higher solubility profile in a variety of mediums, greatly enhancing the baicalein-nicotinamide dissolving rate. *In vivo* tests showed that it outperformed previous BE formulations with a bioavailability that was 6.02-fold higher than BE coarse powder. The study concluded that nano-cocrystals proved to be a highly effective approach to improve the solubility and bioavailability of poorly soluble natural products like BE.[83]

Limitations and challenges

Choosing appropriate co-formers and producing co-crystals on a big scale are two of the many difficulties that come with the intricate and multidimensional process of co-crystal creation. Prediction, screening, synthesis, characterisation, pre-formulation, pharmacokinetic studies (absorption, distribution, metabolism and excretion), formulation, process development, preparation, submission and investigational new drug (IND) application are all steps in the complex process of creating pharmaceutical co-crystals. Ultimately, the process culminates in drug clinical trials.[84] Each step requires careful consideration and expertise to ensure the successful development of co-crystals with enhanced physicochemical properties and therapeutic efficacy.

Co-former selection

One of the most challenging parts of creating co-crystals is selecting the co-former. The knowledge-based technique and the experimental method are mostly used to choose the co-former. Analytical techniques including differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and others are employed to verify the production of cocrystals and the testing procedure is based on trial and error. The resources required for this strategy were substantial. The lattice energy calculation, Hansen's solubility parameter, pKa-based models, supramolecular synthon compatibility utilising the Cambridge Structure Database and thermal analysis are other knowledge-based methods that can be used instead to select suitable co-crystals.[85]

Scale-up of co-crystals

There are no well-established scaling-up techniques for pharmaceutical co-crystal preparation.[44] Numerous techniques, usually carried out in batch processing mode, have been investigated for co-crystallisation manufacture, including solvent-based and dry powder processes. Fixed batch

sizes, several sequential phases, wasteful use of raw materials, lengthy lead times, disruptions and the need for substantial validation and scale-up are some of the drawbacks that batch-level processes frequently encounter. A number of continuous co-crystallisation methods, including as resonant acoustic mixing and hot melt extrusion, have been developed recently. Regulatory bodies encourage the adoption of innovative pharmaceutical processes for continuous production due to the drawbacks of batch-level manufacturing. These continuous methods have demonstrated the ability to produce co-crystals with higher yields, reduced material waste and real-time process monitoring. Additionally, they provide benefits including simpler scaling up, more effective use of equipment, fully automated production, less waste, smaller plant footprints, lower costs, reduced energy consumption, enhanced safety and shorter manufacturing times. As a result, continuous crystallisation is a highly desirable approach, particularly when combined with a quality by design (QbD) strategy.[86]

Challenges in the screening of co-crystals

Solid-state grinding and solvent-based co-crystallisation are the two main categories into which co-crystal preparation methods can be divided. In solvent-based methods, scientists face challenges such as selecting the appropriate solvent and determining optimal cooling and heating profiles. Each approach presents unique obstacles. Solid-state grinding is often preferred for studying co-crystals due to its simplicity and efficiency compared to solvent-based techniques. However, solid-state grinding can sometimes induce phase changes in pharmaceutical co-crystals, which may complicate the process.[87]

Market formulations of co-crystal

The success of co-crystallisation in the pharmaceutical sector is demonstrated by the market's acceptance of drugs made from co-crystals (Table 1). The medications that are on the market that contain co-crystals-based APIs are Suglat®, Entresto® and Steglatro®.[5]

Table 1: Marketed formulations containing co-crystals

Drug name	API	Co-former	Dosage form	Approval year	Manufacturer	Observations	Ref.
Seglentis	Celecoxib	Tramadol	Tablet	2021 FDA	*Kowa Pharmaceutical*, Alabama, United States	Improved bioavailability	[81, 88]
Meyzent	Siponimod	Fumaric acid	Tablet	2019 FDA	*Novartis,* Basel, Switzerland	Improved solubility, thermal stability	[80, 89]
Steglatro	Ertugliflozin	L-pyroglutamic acid	Tablet	2017 FDA	*Pfizer,* New York, United States	Improved stability of Ertugliflozin	[90]
Odomzo	Sonidegib	Phosphoric acid	Tablet	2015 FDA	*Sun Pharma Global,* Mumbai, India	Improved bioavailability, solubility	[91]
Entresto	Sacubitril sodium	Valsartan sodium	Tablet	2015 FDA	*Novartis,* Basel, Switzerland	Improved bioavailability of valsartan by 50 %	[92]
Zafatek	Trelagliptin	Succinic acid	Tablet	2015 Japan	*Takeda Pharmaceutical Company,* Tokyo, Japan	Improved bioavailability, solubility and efficacy	[93]
Suglat	Ipragliflazin	L-proline	Tablet	2014 FDA	*Kotobuki pharmaceutical, Astellaspharma,* Tokyo, Japan	Improved stability against hydrate formation	[94]
Lamivudine /zidovudineTeva	Lamivudine	Zidovudin	Tablet	2011 EMA	*Teva Pharma BV,* Tel Aviv-Yafo, Israel	Improved stability	[34,78]

Most recent patents on cocrystals

Recent advancements in co-crystal engineering have led to numerous patented formulations aimed at enhancing the solubility, stability and bioavailability of API. These patents focus on novel co-former selection strategies, innovative preparation methods such as solvent evaporation, liquid-assisted grinding and supercritical fluid technology, as well as applications in controlled drug release and target delivery. Patents on co-crystals are provided in Table 2, with a co-former, methods of preparation and their uses.

Table 2: Patents on cocrystals

S No	Patent No	Title	Preparation method	Co former	Use	Year	Ref.
1	US20230181507A1	Gabapentin, ketoprofen and lysine, co-crystals and their pharmaceutical compositions and their medical use	Cooling crystallisation method	Drug-drug co-crystals of gabapentin and ketoprofen, lysine	Reduction of pain and/or inflammation	2023	[93]
2	US11717516B2	Co-crystals (Itanapraced)	Liquid assist grinding method and slurry method	Nicotinamide	For treatment of neurodegenerative disorders, infections, dementias, inflammation	2023	[94]
3	US20220324808A1	Co-crystals of compound dihydrochloride and preparation method and use	Solvent evaporation method	Fumaric acid, tartaric acid	Cardiac myosin activator drugs and drugs for treating heart failure	2022	[95]
4	US20230111210A1	Cocrystal antioxidants of protocatechuic acid and l-theanine for the treatment of oxidative stress and inflammation	Liquid assist grinding method	L-theanine	Acute inflammatory disease, chronic inflammatory disease, cardiovascular inflammatory disease, oxidative stress, diabetes.	2023	[96]
5	US20220259189A1	Posaconazole co-crystals, methods of making	Reaction crystallisation method	Aminobenzoic acid (4ABA)	Treatment / prevention of fungal, yeast, or dermatophyte infections	2022	[97]
6	US20220071936A1	Cocrystal of ketoprofen, compositions comprising the same, process of producing the same and uses	Solvent evaporation method and anti-solvent or precipitation method	Lysine	Treatment of pain and inflammatory diseases	2022	[98]
7	WO2022263576A1	Co-crystals of apixaban with a carboxylic acid	Slurry method	Carboxylic acid selected from fumaric acid or an aromatic carboxylic acid	Oral anticoagulant	2022	[99]
8	WO2021044437A1	The procedure of preparing olaparib co-crystals	Cooling crystallisation Method	3,5-dihydroxybenzoic acid with fumaric acid	Treatment of some people with ovarian, breast and BRCA-mutated cancers	2021	[100]

9	WO2021060949A1	Co-crystalline efinaconazole and method for producing the same	Solvent evaporation method	Polyethylene glycol, nicotinamide, fumaric acid, hydroquinone, malonic acid and caffeic acid	Treatment of fungal or yeast infection	2021	[101]
10	US20210277049A1	Progesterone co-crystals, their production process and their application	Liquid assist grinding method and solvent evaporation method	Sophthalic acid, 4-formylbenzeneboronic acid or 3-nitrophthalic	Prevents pregnancy	2021	[102]
11	WO2021137369A1	Novel co-crystals of empagliflozin	Solvent evaporation method and cooling crystallisation	Fumaric acid, citric acid and L-pyruglutamic acid	Treatment of diabetes mellitus	2021	[103]
12	WO2021230198A1	Co-crystals of dihydroquinolinone compound	Anti-solvent method (mixing dihydroquinolinone and one co-former in a solvent, then add this solution in poor solvent)	Gentisic acid or salicylic acid	Treatment of tuberculosis	2018	[104]

Conclusion

Without affecting the medications' inherent activity, the co-crystal approach has become a crucial way to improve their physicochemical characteristics. Co-crystals enhance important pharmacological qualities such solubility, bioavailability, stability and mechanical qualities by taking use of non-covalent interactions between APIs and co-formers. They are therefore a useful tool for resolving formulation issues with poorly soluble medications, especially those in BCS Classes II and IV.

Several preparation methods, such as solvent-based techniques (like solvent evaporation or anti-solvent crystallisation), non-solvent methods (including hot-melt extrusion and grinding) and supercritical fluid technologies, offer scalable and eco-friendly routes for co-crystal production. However, to unlock the full potential of co-crystals, increased focus is necessary, especially on large-scale production. The challenge of scalability in co-crystal production presents a major obstacle, demanding innovative solutions to achieve consistency and cost-effectiveness. For co-crystals to be used more widely in the pharmaceutical industry, these problems must be resolved. Their route to commercialisation is complicated by the FDA and EMA's classification of co-crystals and the need for comprehensive stability and bioequivalence studies.

Co-crystals have enormous potential in medication development, despite a number of obstacles. Their ability to extend patent life, improve therapeutic performance and enable continuous manufacturing processes positions them as a key innovation in modern pharmaceuticals. Future research should focus on optimising scalable production methods, refining predictive modelling for co-former selection and addressing regulatory ambiguities to facilitate broader adoption.

The next generation of medication formulations, which will deliver safer, more effective and patient-compliant medicines, will likely heavily rely on co-crystals as crystal engineering and process optimisation continue to progress. Co-crystals represent an exciting new area in pharmaceuticals that could transform medication delivery and enhance healthcare outcomes worldwide by bridging the gap between molecular design and real-world formulation problems.

Ethics

This review article excludes any new research studies on humans or animals; rather, it is based on a study of previously published material. In order to recognise the original authorship and contributions, all listed sources were appropriately referenced. There are no conflicts of interest related to this work, according to the authors. The content was produced in accordance with ethical publishing guidelines with the intention of advancing the current scientific discussion in the area of drug development. Therefore, the ethics approval was not required in this paper.

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References

1. Ma P, Toussaint B, Roberti EA, Scornet N, Santos Silva A, Castillo Henríquez L, et al. New lidocaine based pharmaceutical cocrystals: preparation, characterization, and influence of the racemic vs enantiopure coformer on the physico chemical properties. Pharmaceutics. 2023;15:1102. doi: 10.3390/pharmaceutics15041102/S1.
2. Lemmerer A, Bernstein J, Griesser UJ, Kahlenberg V, Többens DM, Lapidus SH, et al. A tale of two polymorphic pharmaceuticals: pyrithyldione and propyphenazone and their 1937 co crystal patent. Chem Eur J. 2011;17:13445–60. doi: 10.1002/chem.201100667.
3. Etter MC. Encoding and decoding hydrogen bond patterns of organic compounds. Acc Chem Res. 1990;23:120–6. doi: 10.1021/ar00172a005.
4. Wang X, Du S, Zhang R, Jia X, Yang T, Zhang X. Drug drug cocrystals: opportunities and challenges. Asian J Pharm Sci. 2021;16:307–17. doi: 10.1016/j.ajps.2020.06.004.
5. Duggirala NK, Perry ML, Almarsson Ö, Zaworotko MJ. Pharmaceutical cocrystals: along the path to improved medicines. Chem Commun. 2015;52:640–55. doi: 10.1039/c5cc08216a.
6. Kumar S, Nanda A. Approaches to design of pharmaceutical cocrystals: a review. Mol Cryst Liq Cryst. 2018;667:54–77. doi: 10.1080/15421406.2019.1577462.
7. Nugrahani I, Kumalasari RA, Auli WN, Horikawa A, Uekusa H. Salt cocrystal of diclofenac sodium L proline: structural, pseudopolymorphism, and pharmaceutics performance study. Pharm. 2020;12:690. doi: 10.3390/pharmaceutics12070690.
8. Fukte SR, Wagh MP, Rawat S. Coformer selection: an important tool in cocrystal formation. Int J Pharm Pharm Sci. 2014;6(7):9–14.
9. Childs SL, Stahly GP, Park A. The salt cocrystal continuum: the influence of crystal structure on ionization state. Mol Pharm. 2007;4:323–38. doi: 10.1021/mp0601345.
10. Liu Y, Zhou Z, Ren X, Li T, Wu H, Li Q, et al. Photoinduced self assembled heterostructures of surface charge controlled metal nucleation on supports for stable and

enhanced electrocatalytic hydrogen evolution reaction activity. J Power Sources. 2025;635:236524. doi: 10.1016/j.jpowsour.2025.236524.
11. Almarsson Ö, Zaworotko MJ. Crystal engineering of the composition of pharmaceutical phases: do pharmaceutical co crystals represent a new path to improved medicines? Chem Commun. 2004:1889–96. doi: 10.1039/b402150a.
12. Othman MF, Jamburi N, Anuar N, Abd Rahim S, Rohalim NH. Ibuprofen amino acids co crystal screening via co grinding methods. MATEC Web Conf. 2016;69:03002. doi: 10.1051/matecconf/20166903002.
13. Sathisaran I, Dalvi SV. Engineering cocrystals of poorly water soluble drugs to enhance dissolution in aqueous medium. Pharm. 2018;10:108. doi: 10.3390/pharmaceutics10030108.
14. Fleischman SG, Kuduva SS, McMahon JA, Moulton B, Bailey Walsh RD, Rodríguez Hornedo N, et al. Crystal engineering of the composition of pharmaceutical phases: multiple component crystalline solids involving carbamazepine. Cryst Growth Des. 2003;3:909–19. doi: 10.1021/cg034035x.
15. Chen T, Tu L, Wang G, Qi N, Wu W, Zhang W, et al. Multi functional chitosan polymeric micelles as oral paclitaxel delivery systems for enhanced bioavailability and anti tumor efficacy. Int J Pharm. 2020;578:119105. doi: 10.1016/j.ijpharm.2020.119105.
16. Wu W, Grohganz H, Rades T, Löbmann K. Comparison of co former performance in co amorphous formulations: single amino acids, amino acid physical mixtures, amino acid salts and dipeptides as co formers. Eur J Pharm Sci. 2021;156:105582. doi: 10.1016/j.ejps.2020.105582.
17. Rocha B, de Morais LA, Viana MC, Carneiro G. Promising strategies for improving oral bioavailability of poor watersoluble drugs. Expert Opin Drug Discov. 2023;18:615–27. doi: 10.1080/17460441.2023.2211801.
18. Ciccone L, Tonali N, Nencetti S, Orlandini E. Natural compounds as inhibitors of transthyretin amyloidosis and neuroprotective agents: analysis of structural data for future drug design. J Enzyme Inhib Med Chem. 2020 Dec;35(1):1145-62. doi: 10.1080/14756366.
19. Bolla G, Sarma B, Nangia AK. Crystal engineering of pharmaceutical cocrystals in the discovery and development of improved drugs. Chem Rev. 2022;122:11514–603. doi: 10.1021/acs.chemrev.1c00987.
20. Gröls JR, Castro Dominguez B. Intelligent mechanochemical design of co amorphous mixtures. Cryst Growth Des. 2022;22:2989–96. doi: 10.1021/acs.cgd.1c01442.
21. Kumar Bandaru R, Rout SR, Kenguva G, Gorain B, Alhakamy NA, Kesharwani P, et al. Recent advances in pharmaceutical cocrystals: from bench to market. Front Pharmacol. 2021;12:780582. doi: 10.3389/fphar.2021.780582.
22. Pindelska E, Sokal A, Kolodziejski W. Pharmaceutical cocrystals, salts and polymorphs: advanced characterization techniques. Adv Drug Deliv Rev. 2017;117:111–46. doi: 10.1016/j.addr.2017.09.014.
23. Guo M, Sun X, Chen J, Cai T. Pharmaceutical cocrystals: a review of preparations, physicochemical properties and applications. Acta Pharm Sin B. 2021;11:2537–64. doi: 10.1016/j.apsb.2021.03.030.
24. Kavanagh ON, Croker DM, Walker GM, Zaworotko MJ. Pharmaceutical cocrystals: from serendipity to design to application. Drug Discov Today. 2019;24:796–804. doi: 10.1016/j.drudis.2018.11.023.
25. Wyatt AJ, Leonard GD, Sachs DL. Cutaneous reactions to chemotherapy and their management. Am J Clin Dermatol. 2006;7:45–63. doi: 10.2165/00128071-200607010-00005.
26. Manin AN, Drozd KV, Churakov AV, Perlovich GL. Hydrogen bond donor/acceptor ratios of the coformers: do they really matter for the prediction of molecular packing in cocrystals? The case of benzamide derivatives with dicarboxylic acids. Cryst Growth Des. 2018;18:5254–69. doi: 10.1021/acs.cgd.8b00711.
27. Ngilirabanga JB, Samsodien H. Pharmaceutical co crystal: an alternative strategy for enhanced physicochemical properties and drug synergy. Nano Sel. 2021;2:512–26. doi: 10.1002/nano.202000201.
28. Das B, Nayak AK, Mallick S. Thyme oil containing fluconazole loaded transferosomal bigel for transdermal delivery. AAPS PharmSciTech. 2023;24:xx. doi: 10.1208/s12249-023-02698-2.
29. Surov AO, Ramazanova AG, Voronin AP, Drozd KV, Churakov AV, Perlovich GL. Virtual screening, structural analysis, and formation thermodynamics of carbamazepine cocrystals. Pharmaceutics. 2023;15:803? (article number not provided). doi: 10.3390/pharmaceutics15030836.
30. Aitipamula S, Chow PS, Tan RBH. Polymorphism in cocrystals: a review and assessment of its significance. CrystEngComm. 2014;16:3451–65. doi: 10.1039/c3ce42008f.
31. Arunan E, Desiraju GR, Klein RA, Sadlej J, Scheiner S, Alkorta I, et al. Definition of the hydrogen bond (IUPAC Recommendations 2011). Pure Appl Chem. 2011;83:1637–41. doi: 10.1351/pac rec 10 01 02.
32. C EM. Hydrogen bonds as design elements in organic chemistry. J Phys Chem. 1991;95:4601–10. doi: 10.1021/j100165a007.
33. Donohue J. The hydrogen bond in organic crystals. J Phys Chem. 1952;56:502–10. doi: 10.1021/j150496a023.
34. Haskins MM, Zaworotko MJ. Screening and preparation of cocrystals: a comparative study of mechanochemistry vs slurry methods. Cryst Growth Des. 2021;21:4141–50. doi: 10.1021/acs.cgd.1c00418.
35. O'Malley C, McArdle P, Erxleben A. Formation of salts and molecular ionic cocrystals of fluoroquinolones and α,ω dicarboxylic acids. Cryst Growth Des. 2022;22:3060–71. doi: 10.1021/acs.cgd.1c01509.
36. Radha Rani E, Venkata Radha G. Engineering cocrystals of paliperidone with enhanced solubility and dissolution characteristics. Arh Farm (Belgr). 2021;71:393–409. doi: 10.5937/arhfarm71-32997.
37. Stanton SA, Du JJ, Lai F, Stanton G, Hawkins BA, Ong JA, et al. Understanding hygroscopicity of theophylline via a novel cocrystal polymorph: a charge density study. J Phys Chem A. 2021;125:9736–56. doi: 10.1021/acs.jpca.0c09536.
38. Chan HCS, Kendrick J, Neumann MA, Leusen FJJ. Towards ab initio screening of co crystal formation through lattice energy calculations and crystal structure prediction of nicotinamide, isonicotinamide, picolinamide and paracetamol multi component crystals. CrystEngComm. 2013;15:3799–807. doi: 10.1039/c3ce40107c.
39. Marchese Robinson RL, Geatches D, Morris C, MacKenzie R, Maloney AGP, Roberts KJ, et al. Evaluation of

force field calculations of lattice energies on a large public dataset, assessment of pharmaceutical relevance, and comparison to density functional theory. J Chem Inf Model. 2019;59:4778–92. doi: 10.1021/acs.jcim.9b00601.
40. Kuminek G, Cao F, Bahia de Oliveira da Rocha A, Gonçalves Cardoso S, Rodríguez Hornedo N. Cocrystals to facilitate delivery of poorly soluble compounds beyond rule of 5. Adv Drug Deliv Rev. 2016;101:143–66. doi: 10.1016/j.addr.2016.04.022.
41. Cambridge Structural Database System | Computing. [Internet]. n.d. [Cited: 24-Jun-25]. Available from: https://www.ch.cam.ac.uk/computing/software/cambridge-structural-database-system.
42. Thakuria R, Sarma B, Nangia A. Hydrogen bonding in molecular crystals. Compr Supramol Chem II. 2017;7:25–48. doi: 10.1016/B978-0-12-409547-2.12598-3.
43. Devogelaer JJ, Meekes H, Tinnemans P, Vlieg E, de Gelder R. Co crystal prediction by artificial neural networks. Angew Chem Int Ed. 2020;59:21711–8. doi: 10.1002/anie.202009467.
44. Heng T, Yang D, Wang R, Zhang L, Lu Y, Du G. Progress in research on artificial intelligence applied to polymorphism and cocrystal prediction. ACS Omega. 2021;6:15543–50. doi: 10.1021/acsomega.1c01330.
45. Wang D, Yang Z, Zhu B, Mei X, Luo X. Machine learning guided cocrystal prediction based on large data base. Cryst Growth Des. 2020;20:6610–21. doi: 10.1021/acs.cgd.0c00767.
46. Wang L, Yan Y, Zhang X, Zhou X. Novel pharmaceutical cocrystal of lenalidomide with nicotinamide: structural design, evaluation, and thermal phase transition study. Int J Pharm. 2022;613:121394. doi: 10.1016/j.ijpharm.2021.121394.
47. Kumar A, Nanda A. In silico methods of cocrystal screening: a review on tools for rational design of pharmaceutical cocrystals. J Drug Deliv Sci Technol. 2021;63:102527. doi: 10.1016/j.jddst.2021.102527.
48. Bennett AJ, Matzger AJ. Progress in predicting ionic cocrystal formation: the case of ammonium nitrate. Chem Eur J. 2023;29:xx. doi: 10.1002/chem.202300076.
49. Mswahili ME, Lee MJ, Martin GL, Kim J, Kim P, Choi GJ, et al. Cocrystal prediction using machine learning models and descriptors. Appl Sci. 2021;11:1323. doi: 10.3390/app11031323.
50. Vologzhanina AV. Intermolecular interactions in functional crystalline materials: from data to knowledge. Cryst. 2019;9:478. doi: 10.3390/cryst9090478.
51. Khan HW, Elgharbawy AAM, Bustam A, Moniruzzaman M. Design and selection of ionic liquids via COSMO for pharmaceuticals and medicine. In: Applied Ionic Liquids for Drug Delivery. 2021. p. 137–64. doi: 10.1007/978-981-16-4365-1_8.
52. Wu D, Zhang B, Yao Q, Hou B, Zhou L, Xie C, et al. Evaluation on cocrystal screening methods and synthesis of multicomponent crystals: a case study. Cryst Growth Des. 2021;21:4531–46. doi: 10.1021/acs.cgd.1c00415.
53. Bysouth SR, Bis JA, Igo D. Cocrystallization via planetary milling: enhancing throughput of solid state screening methods. Int J Pharm. 2011;411:169–71. doi: 10.1016/j.ijpharm.2011.03.037.
54. Trivedi HR, Borkar DS, Puranik PK. Experimental design approach for development of cocrystals and immediate release cocrystal tablet of atorvastatin calcium for enhancement of solubility and dissolution. J Res Pharm. 2020;226. doi: 10.35333/jrp.2020.226.
55. Karagianni A, Malamatari M, Kachrimanis K. Pharmaceutical cocrystals: new solid phase modification approaches for the formulation of APIs. Pharmaceutics. 2018;10:18. doi: 10.3390/pharmaceutics10010018.
56. Douroumis D, Ross SA, Nokhodchi A. Advanced methodologies for cocrystal synthesis. Adv Drug Deliv Rev. 2017;117:178–95. doi: 10.1016/j.addr.2017.07.008.
57. Dal Magro C, dos Santos AE, Ribas MM, Aguiar GPS, Volfe CRB, Lopes MLLC, et al. Production of curcumin resveratrol cocrystal using cocrystallization with supercritical solvent. J Supercrit Fluids. 2021;171:105190. doi: 10.1016/j.supflu.2021.105190.
58. Saraf GJ, Burade KKB, Gonjari ID, Hosmani AH, Pawar AA. A review on advances in pharmaceutical co crystal preparation routes, intellectual property perspective and regulatory aspects. Int J Curr Pharm Res. 2022:4–12. doi: 10.22159/ijcpr.2022v14i5.2038.
59. Jung S, Choi I, Kim IW. Liquid assisted grinding to prepare a cocrystal of adefovir dipivoxil thermodynamically less stable than its neat phase. Crystals. 2015;5:583–91. doi: 10.3390/cryst5040583.
60. Karimi Jafari M, Padrela L, Walker GM, Croker DM. Creating cocrystals: a review of pharmaceutical cocrystal preparation routes and applications. Cryst Growth Des. 2018;18:6370–87. doi: 10.1021/acs.cgd.8b00933.
61. Narala S, Nyavanandi D, Alzahrani A, Bandari S, Zhang F, Repka MA. Creation of hydrochlorothiazide pharmaceutical cocrystals via hot melt extrusion for enhanced solubility and permeability. AAPS PharmSciTech. 2022;23:xx. doi: 10.1208/s12249-021-02202-8.
62. Pawar N, Saha A, Nandan N, Parambil JV. Solution cocrystallization: a scalable approach for cocrystal production. Cryst. 2021;11:303. doi: 10.3390/cryst11030303.
63. Wicaksono Y, Setyawan D, Siswandono. Formation of ketoprofen malonic acid cocrystal by solvent evaporation method. Indones J Chem. 2017;17:161–6. doi: 10.22146/ijc.24884.
64. Urano M, Kitahara M, Kishi K, Goto E, Tagami T, Fukami T, et al. Physical characteristics of cilostazol–hydroxybenzoic acid cocrystals prepared using a spray drying method. Cryst. 2020;10:313. doi: 10.3390/cryst10040313.
65. Setyawan D, Oktavia IP, Farizka R, Sari R. Physicochemical characterization and in vitro dissolution test of quercetin-succinic acid co-crystals prepared using solvent evaporation. Turk J Pharm Sci. 2017 Dec;14(3):280-284. doi: 10.4274/tjps.16362.
66. Zu'aimah Barikah K. Traditional and novel methods for cocrystal formation: a mini review. Syst Rev Pharm. n.d.;9:xx. doi: 10.5530/srp.2018.1.15.
67. Wang IC, Lee MJ, Sim SJ, Kim WS, Chun NH, Choi GJ. Anti solvent co crystallization of carbamazepine and saccharin. Int J Pharm. 2013;450:311–22. doi: 10.1016/j.ijpharm.2013.04.012.
68. Aghara M, Dudhat K. Solubility and dissolution enhancement of luliconazole by a cocrystal engineering technique with different coformers. J Pharm Innov. 2023;18:1701–12. doi: 10.1007/s12247-023-09751-4.
69. Wasim M, Mannan A, Asad MHH Bin, Amirzada MI, Shafique M, Hussain I. Fabrication of carbamazepine co-

crystals: characterization, in vitro and comparative in vivo evaluation. Biomed Res Int. 2021;2021:6685806. doi: 10.1155/2021/6685806.
70. Biscaia IFB, Oliveira PR, Gomes SN, Bernardi LS. Obtaining cocrystals by reaction crystallization method: pharmaceutical applications. Pharmaceutics. 2021;13:898. doi: 10.3390/pharmaceutics13060898.
71. Vaksler YA, Benedis D, Dyshin AA, Oparin RD, Correia NT, Capet F, et al. Spectroscopic characterization of single co-crystal of mefenamic acid and nicotinamide using supercritical CO2. J Mol Liq. 2021;334:116117. doi: 10.1016/j.molliq.2021.116117.
72. Chakravarty P, Famili A, Nagapudi K, Al-Sayah MA. Using supercritical fluid technology as a green alternative during the preparation of drug delivery systems. Pharmaceutics. 2019;11:629. doi: 10.3390/pharmaceutics11120629.
73. Saganowska P, Wesolowski M. DSC as a screening tool for rapid co-crystal detection in binary mixtures of benzodiazepines with co-formers. J Therm Anal Calorim. 2018;133:785–95. doi: 10.1007/s10973-017-6858-3.
74. Dhondale MR, Thakor P, Nambiar AG, Singh M, Agrawal AK, Shastri NR, et al. Co-crystallization approach to enhance the stability of moisture-sensitive drugs. Pharmaceutics. 2023;15:189. doi: 10.3390/pharmaceutics15010189.
75. Chen Y, Li L, Yao J, Ma YY, Chen JM, Lu TB. Improving the solubility and bioavailability of apixaban via apixaban-oxalic acid cocrystal. Cryst Growth Des. 2016;16:2923–30. doi: 10.1021/acs.cgd.6b00266.
76. Shaikh R, Singh R, Walker GM, Croker DM. Pharmaceutical cocrystal drug products: an outlook on product development. Trends Pharmacol Sci. 2018;39:1033–48. doi: 10.1016/j.tips.2018.10.006.
77. Singh M, Barua H, Jyothi VGSS, Dhondale MR, Nambiar AG, Agrawal AK, et al. Cocrystals by design: a rational coformer selection approach for tackling the API problems. Pharmaceutics. 2023;15:1161. doi: 10.3390/pharmaceutics15041161.
78. Chavan RB, Thipparaboina R, Yadav B, Shastri NR. Continuous manufacturing of co-crystals: challenges and prospects. Drug Deliv Transl Res. 2018;8:1726–39. doi: 10.1007/s13346-018-0479-7.
79. Chow PS, Lau G, Ng WK, Vangala VR. Stability of pharmaceutical cocrystal during milling: a case study of 1:1 caffeine-glutaric acid. Cryst Growth Des. 2017;17:4064–71. doi: 10.1021/acs.cgd.6b01160.
80. Díaz-Villamarín X, Piñar-Morales R, Barrero-Hernández FJ, Antúnez-Rodríguez A, Cabeza-Barrera J, Morón-Romero R. Pharmacogenetics of siponimod: a systematic review. Biomed Pharmacother. 2022;153:113536. doi: 10.1016/j.biopha.2022.113536.
81. Ashrafizadeh M, Tavakol S, Ahmadi Z, Roomiani S, Mohammadinejad R, Samarghandian S. Therapeutic effects of kaempferol affecting autophagy and endoplasmic reticulum stress. Phytother Res. 2020;34:911–23. doi: 10.1002/ptr.6577.
82. Niu J, Wang L, Yuan M, Zhang J, Chen H, Zhang Y. Dual-targeting nanocarrier based on glucose and folic acid functionalized Pluronic P105 polymeric micelles for enhanced brain distribution. J Drug Deliv Sci Technol. 2020;57:101343. doi: 10.1016/j.jddst.2019.101343.
83. Wang Y, Liu S, Dong W, Qu X, Huang C, Yan T, et al. Combination of hesperetin and platinum enhances anticancer effect on lung adenocarcinoma. Biomed Pharmacother. 2019;113:108779. doi: 10.1016/j.biopha.2019.108779.
84. Wu Z, Li C, Chen Y, Liu Q, Li N, He X, et al. Chrysin protects against titanium particle-induced osteolysis by attenuating osteoclast formation and function by inhibiting NF-κB and MAPK signaling. Front Pharmacol. 2022;13:793087. doi: 10.3389/fphar.2022.793087.
85. Geng A, Xu S, Yao Y, Qian Z, Wang X, Sun J, et al. Chrysin impairs genomic stability by suppressing DNA double-strand break repair in breast cancer cells. Cell Cycle. 2022;21:379–91. doi: 10.1080/15384101.2021.2020434.
86. Dewi RM, Megawati M, Antika LD. Antidiabetic properties of dietary chrysin: a cellular mechanism review. Mini Rev Med Chem. 2021;22:1450–7. doi: 10.2174/1389557521666211101162449.
87. Khan A, Ikram M, Hahm JR, Kim MO. Antioxidant and anti-inflammatory effects of citrus flavonoid hesperetin: special focus on neurological disorders. Antioxidants (Basel). 2020;9:609. doi: 10.3390/antiox9070609.
88. O'Sullivan A, Long B, Verma V, Ryan KM, Padrela L. Solid-state and particle size control of pharmaceutical cocrystals using atomization-based techniques. Int J Pharm. 2022;621:121798. doi: 10.1016/j.ijpharm.2022.121798.
89. U.S. Food and Drug Administration. Drug trials snapshots: MAYZENT. [Internet]. n.d. Available from: [Cited: 24-Jun-25]. https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-mayzent.
90. Jin YR, Han XH, Zhang YH, Lee JJ, Lim Y, Kim TJ, et al. Hesperetin, a bioflavonoid, inhibits rat aortic vascular smooth muscle cells proliferation by arresting cell cycle. J Cell Biochem. 2008;104:1–14. doi: 10.1002/jcb.21592.
91. Huang J, Li Y, Huang RK, He CT, Gong L, Hu Q, et al. Electrochemical exfoliation of pillared-layer metal–organic framework to boost the oxygen evolution reaction. Angew Chem Int Ed. 2018;57:4632–6. doi: 10.1002/anie.201801029.
92. Wu D, Cao XH, Jia PZ, Zeng YJ, Feng YX, Tang LM, et al. Excellent thermoelectric performance in weak-coupling molecular junctions with electrode doping and electrochemical gating. Sci China Phys Mech Astron. 2020;63:1–11. doi: 10.1007/s11433-019-1528-y.
93. Aramini A, Bianchini G, Lillini S, Tomassetti M, Pacchiarotti N, Canestrari D, et al. Ketoprofen, lysine and gabapentin co-crystal magnifies synergistic efficacy and tolerability of the constituent drugs: pre-clinical evidences towards an innovative therapeutic approach for neuroinflammatory pain. Biomed Pharmacother. 2023;163:114845. doi: 10.1016/j.biopha.2023.114845.
94. Müller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy: rationale for development and what we can expect for the future. Adv Drug Deliv Rev. 2001;47:3–19. doi: 10.1016/S0169-409X(00)00118-6.
95. US20220324808A1. Co-crystal of compound I dihydrochloride and preparation method and use thereof. Google Patents [Internet]. n.d. [Cited: 25-Jun-25]. Available from: https://patents.google.com/patent/US20220324808A1/en.
96. US20230201147A1. Cocrystal antioxidants of protocatechuic acid with L-theanine for the treatment of oxidative stress and inflammatory conditions. Google Patents [Internet]. n.d. [Cited: 25-Jun-25].

Available from: https://patents.google.com/patent/US20230201147A1/en.
97. WO2021022103A1. Cocrystals of posaconazole, methods of making and using same. Google Patents [Internet]. n.d. [Cited: 25-Jun-25]. Available from: https://patents.google.com/patent/WO2021022103A1/en.
98. US12285396B2. Co-crystal of ketoprofen, compositions comprising the same, process of producing the same, and uses thereof. Google Patents [Internet]. n.d. [Cited: 25-Jun-25]. Available from: https://patents.google.com/patent/US12285396B2/en.
99. WO2022263576A1. Co-crystal of apixaban with a carboxylic acid. Google Patents [Internet]. n.d. [Cited: 25-Jun-25]. Available from: https://patents.google.com/patent/WO2022263576A1/en.
100. Pathi SL, Chennuru R, Bollineni M. Olaparib co-crystals and process of preparation thereof. 2021.
101. WO2021060949A1. Co-crystalline efinaconazole, and method for producing same. Google Patents [Internet]. n.d. [Cited: 25-Jun-25]. Available Available from: https://patents.google.com/patent/WO2021060949A1/en.
102. US20210277049A1. Cocrystal of progesterone and preparation method and use thereof. Google Patents [Internet]. n.d. [Cited: 25-Jun-25]. Available Available from: https://patents.google.com/patent/US20210277049A1/en.
103. WO2021137369A1. Novel cocrystal of empagliflozin. Google Patents [Internet]. n.d. [Cited: 25-Jun-25]. Available Available from: https://patents.google.com/patent/WO2021137369A1/en.
104. WO2021230198A1. Cocrystal of dihydroquinolinone compound. Google Patents [Internet]. n.d. [Cited: 25-Jun-25]. Available from: https://patents.google.com/patent/WO2021230198A1/en.