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Review Article

Exploration of Pharmaceutical Cocrystals of Zaltoprofen: Development, Physicochemical Characterization, and Enhancement of Solubility and Dissolution Behavior

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Abstract

Biopharmaceutics Classification System (BCS) Class II drugs are characterized by low aqueous solubility, which can limit dissolution and oral absorption. Zaltoprofen is a non-steroidal anti-inflammatory drug with a hydrophobic structure and limited aqueous solubility. Pharmaceutical cocrystallization offers a solid-state strategy for modifying lattice packing and physicochemical properties without altering the covalent structure of the active pharmaceutical ingredient. This review summarizes principles of cocrystal design, coformer selection, preparation methods, solid-state characterization, and the effects of cocrystallization on solubility and dissolution behavior, with particular emphasis on zaltoprofen. Solution-based crystallization, mechanochemical approaches such as liquid-assisted grinding, and emerging continuous-processing approaches including hot-melt extrusion are discussed. The review also emphasizes that improved dissolution is not guaranteed and may be limited by lattice stability, supersaturation loss, or solution-mediated phase transformation. Translational success will therefore depend on rational coformer selection, robust solid-state characterization, scalable manufacturing, and appropriate in vitro and in vivo validation. The review further considers the use of coformers such as nicotinamide and 4,4′-bipyridine, while emphasizing that dissolution enhancement is system-dependent and must be demonstrated experimentally.

Keywords: Zaltoprofen, Pharmaceutical cocrystals, BCS class II drug , Solubility Enhancement

1. Introduction

The drug delivery system is challenged due to poor aqueous solubility which continues to plague the successful development of many therapeutic agents. Many drug candidates of modern time show low intrinsic solubility, which affects dissolution behaviour and results in poor oral bioavailability [1]. According to the Biopharmaceutics Classification System (BCS), the compounds may be classified as Class II drugs having high membrane permeability but poor aqueous solubility. The solubilization of such drugs becomes the rate-limiting step for gastrointestinal absorption and may result in incomplete absorption of drug; high pharmacokinetic heterogeneity and undependable therapeutic outcome [2].NSAIDs are among the most widely prescribed drug classes for the treatment of pain and inflammatory disorders. Many NSAIDs contain weakly acidic functional groups with lipophilic aromatic structures, which impede their aqueous solubility under physiological conditions [3]. As a result, dissolution kinetics often control their absorption rather than permeability. From a formulation perspective, a higher dose or advanced formulation approaches are often required, which can further create stability and manufacturability issues as well as dose-dependent toxicity issues.Various formulation strategies have been devised to counter solubility-limited drug absorption through particle size reduction, salt formation, amorphous solid dispersion, lipid-based delivery systems, and molecular complexation [4]. These are also the most common approaches in the pharmaceutical industry. Though these techniques can improve their dissolution, they often come with problems as instability of the chemical, recrystallization, processing difficulty, scale-up difficulty, etc. Alternative solid-state strategies are required to improve solubility without compromising structural integrity, these limitations indicate so [5]. Given this, pharmaceutical cocrystals have now emerged as an efficient and flexible approach for improving the physicochemical behaviour of poorly soluble drugs.

Zaltoprofen is a non-steroidal anti-inflammatory drug that is derived from propionic acids. It is used for treating inflammatory and musculo-skeletal conditions

like – osteoarthritis, rheumatoid arthritis, post-operative pain in adults and children [6]. The drug acts mainly by inhibition of cyclooxygenase (COX) enzymes leading to decreased synthesis of prostaglandins and reduced inflammation [7]. Moreover, the analgesic effect of zaltoprofen may be partly due to its action on bradykinin nociceptive pathways.

The pharmaceutical performance of zaltoprofen may be limited by its poor aqueous solubility. Furthermore, its absorption is dissolution-limited. All of this shows that zaltoprofen is a BCS Class II drug. Because of its hydrophobic aromatic framework and weakly acidic carboxylic group, zaltoprofen has limited solubility in aqueous physiological media [8]. Therefore, zaltoprofen has a slow dissolution, a delayed onset of action, and variable bioavailability.

Multiple formulation strategies, such as micronization, solid dispersions and inclusion complexes were evaluated to enhance its dissolution. However, these strategies are often limited either due to the inability of the physical systems to keep up with the design or due to processing problems [9]. Similarly, some of them fail to significantly enhance drug solubility. As a result, the alteration of solid-state properties of zaltoprofen could improve its drug performance.

1.1 Pharmaceutical Cocrystals as a Solid-State Modification Strategy

Pharmaceutical cocrystals are crystalline entities made of multiple components, usually one active pharmaceutical ingredient (API) and one or more neutral coformers in which the component molecules are arranged in a single lattice through non-covalent interactions, such as typically hydrogen bonding [10]. Unlike salts, which involve proton transfer, cocrystals consist of neutral molecules which interact through supramolecular synthons to furnish a new crystalline phase with distinct physicochemical properties.

The main benefit of cocrystal engineering is the capacity to modify the intermolecular interactions inside the crystal lattice that affects various solid-state properties such as solubility, dissolution rate, melting behaviour and mechanical properties without chemically altering the drug molecule. Unlike other solid-state approaches such as polymorphs, solvates and amorphous systems, cocrystals provide a more stable, and structurally ordered platform for property optimization [11] .

Pharmaceutical cocrystals have gained a lot of interest as a strategy to enhance the solubility and bioavailability of poorly soluble drugs in recent years. A large number of studies show that rational coformer selection and crystal engineering can substantially improve dissolution behavior [12]. This is indicative of the increasing significance of cocrystals.

The rise in poorly soluble drug candidates has increased the demand for new solid-state approaches that can enhance performance without undue formulation complexity. Zaltoprofen is a suitable model compound for such studies as its therapeutic efficacy is predominantly controlled by dissolution-controlled absorption [13].

The presence of functional groups, which can engage in hydrogen bonding, suggests that zaltoprofen may undergo cocrystallization with an appropriate pharmaceutically acceptable coformer. Recent studies present different techniques (methods) and coformers used to develop zaltoprofen cocrystals to enhance its solubility/dissolution profile [14]. Unfortunately, however, all the information is scattered over different reports.Consequently, the objective of this review is to critically summarize recent advances in the design, preparation and characterization of zaltoprofen pharmaceuticals cocrystals [15]. Special focus will be given to strategies for selectively choosing coformers, crystal engineering principles, preparation methods, and characterization methods to confirm the cocrystal(Figure 1.). The current review also discusses the impact of cocrystal formation on solubility enhancement and dissolution behaviour and pharmaceutical performance [16]. Also, it points out the existing challenges and future opportunities for research and development.

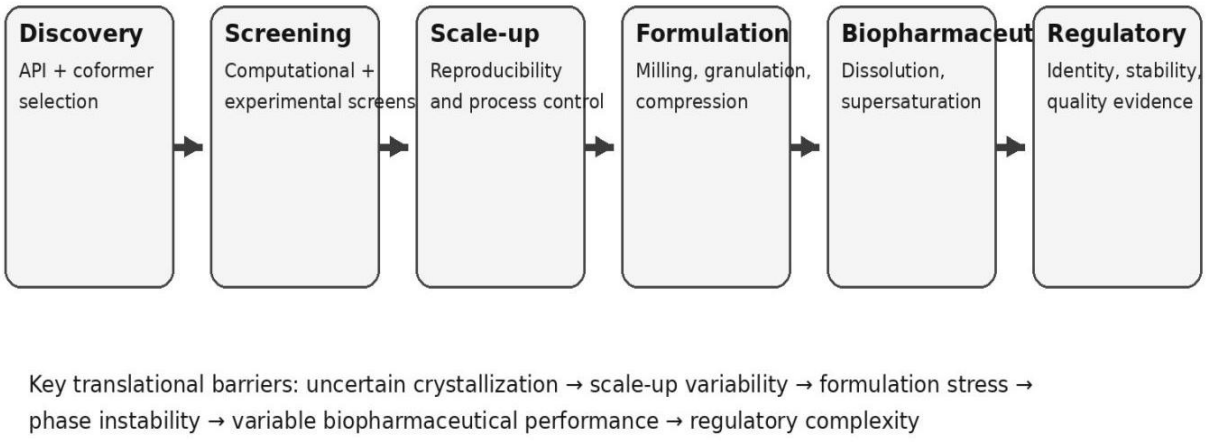

Figure 1. Translational pathway for pharmaceutical cocrystal development, from molecular discovery and screening through scale-up, formulation, biopharmaceutical assessment, and regulatory evaluation. Schematic redrawn by the authors based on published cocrystal-development principles.[10–16]

2. Fundamentals of Pharmaceutical Cocrystals

Pharmaceutical cocrystals can defined as ordered formations of an active pharmaceutical ingredient (API) and neutral coformers in fixed stoichiometric ratio which are stabilized due to the non-covalent interaction [17]. In addition, the formation does not affect the chemical structure of the API. Changing the configuration of crystals allows us to change the solubility, dissolution, mechanical properties and stability of a material. However, not all co-formers will work. Enhancement of drug solubility/solubility rate is highly context-dependent, influencing coformers, polymer environment, and lattice robustness.

Unlike salts, which are reliable because of their predictable ionic interactions with cations, cocrystals rely on subtler and more directionally specific forces, which renders their formation intrinsically uncertain a priori [18]. Various novel solid-state approaches such as solvates, polymorphs, co-amorphous systems can also be used to modulate these and other properties(Figure 2.). Notably, they all have limitations: solvates may destabilize through loss of solvent, modification options are limited for polymorphs and co-amorphous systems may crystallize rapidly [19].

Cocrystals occupy an important niche in solid-state pharmaceutical design; however, claims of superiority over other solid forms should be supported by direct comparative studies.

Molecular interactions and supramolecular synthons.

Cocrystal assembly is guided by supramolecular synthons. Supramolecular synthons are recurrent patterns of intermolecular interaction. The interactions are primarily hydrogen bonds; however, other interactions such as π–π stacking, van der Waals, dipolar etc. are also present [20]. Although designs can be complex, crystallization is the most unpredictable task in chemistry. Avoiding overall crystallization can result from slight changes in solvent, temperature or stoichiometry. A number of rationally designed co-crystals have not been able to be scaled up for manufacture, illustrating a discrepancy between the theory and practice[21] .

Regulatory perspective: FDA and EMA

Regulatory classification differs from that of a new covalent API; therefore, the identity, stability, phase purity, and pharmaceutical performance of a cocrystal must be adequately characterized for development and regulatory assessment. The minimum evidence should include the stability of shape, a separate crystalline phase, and others. Many efforts are being made to develop a draft regulatory framework for characterising complex drug formulations [22]. However, other issues of importance, such as the borderline case of salts versus cocrystals; dissociation kinetics and longer-term stability are not well understood and need integrated chemistry/formulation/regulatory actions to realise true therapeutic benefit.

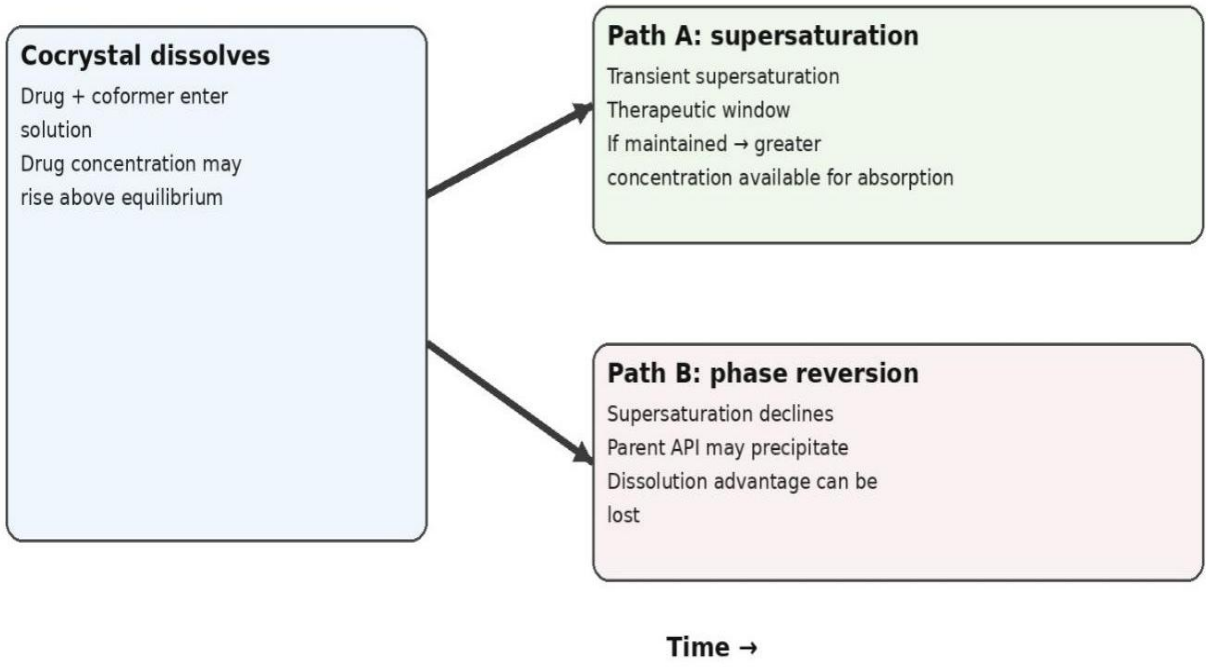

Figure 2. Multiscale architecture of cocrystal design, linking supramolecular interactions and crystal lattice structure with particle properties, dissolution behavior, and potential clinical performance. Schematic redrawn by the authors based on published solid-state and pharmaceutical cocrystal literature.[10–12,57]

3. Design and Screening of Zaltoprofen Cocrystals

3. 1 Selection Criteria for Coformers

The success of cocrystal formation depends on choosing the right coformer that forms energetically favourable and structurally compatible interaction with API. Coformers must be not only supramolecularly complementary but also physicochemical compatible and regulatory safe, which often leads to a preference for GRAS or established excipients to minimize risk of translation [23].

The potential for molecular interactions is a key determinant of salt and cocrystal formation can be predicted using ΔpKa to some extent, but this guideline is an oversimplification of reality. Lattice energy, packing preferences, and various competing interactions often overshadow acid–base predictions, resulting in different outcomes in practice [24]. The hydrogen-bond donor–acceptor complementarity, π–π stacking, and molecular shape complementarity are equally important as seen in zaltoprofen where the carboxylic acid and aromatic scaffold allow strong interactions with amide- or heterocyclic-containing coformers. Several coformer-selection criteria exist but coformer selection is highly uncertain as the parent crystal stability often resists the heteromolecular assembly and therefore, it is crucial to validate the existence of the desired crystal experimentally [25].

Methods for Screening Cocrystal Formation

Due to the complex interplay of thermodynamics and crystallization kinetics, screening should be systematic. Modeling tools such as Hansen solubility parameters, molecular modeling, and crystal structure prediction give a first estimate as to whether molecules will be compatible and furthermore whether there will be any local hydrogen-bonding networks [26]. However, they do not take full account of lattice energetic implications or nucleation difficulties.

Hence, experimental approaches are vital. Neat grinding and liquid-assisted grinding are mechanochemical methods that can quickly determine whether a cocrystal will form [27]. On the other hand, solution-mediated methods (solvent evaporation, cooling crystallization, and slurry conversion) control lattice growth through growth from a solvent or solvent mixture that can dissolve both solid components at appropriate temperatures and concentrations [28]. Effective identification of successful conditions usually requires iterations. Structural and solid-state characterizations are then done.

3. 2 Reported Coformers for Zaltoprofen

Research on zaltoprofen cocrystals has focused on coformers that can interact with its carboxylic acid and aromatic regions. The amide functionality of nicotinamide usually forms hydrogen bonded synthons which reorganize the crystal lattice and may modulate dissolution [29]. The presence of hydrogen-bond acceptors as well as aromatic rings in 4,4′-bipyridine as a consequence pi–pi stacking influences the packing and stability of the lattice(Table 1).

Formation of cocrystals does not necessarily lead to enhanced drug performance which is contrary to the expectations [30]. Increased lattice stabilization can potentially impede dissolution. Further, there are only a few systematically characterized zaltoprofen cocrystals which makes it difficult to fully understand the structure-property relationships. To decide if cocrystal engineering can create a pharmaceutical advantage, expanding coformer diversity and evaluating dissolution kinetics, thermodynamic stability and processability are important [31].

Table 1: Rational Supramolecular Design of Zaltoprofen Cocrystals [29–31]

Coformer	**Target Functional Group**	**Key Molecular Synthon**	Mechanistic Significance	Reference (s)
Nicotinamide	Carboxylic acid moiety	Acid–Amide Heterosynthon	Promotes structural reorganization, enhancing solubility.	[29]
4,4′-Bipyridine	Carboxylic acid moiety	Acid–Pyridine Heterosynthon	Stabilizes the lattice through π–π stacking interactions.	[30]
Aromatic Amines	Carboxylic acid group	Acid–Heterocycle Synthon	Optimizes molecular complementarity for tighter packing.	[31]

4. Preparation Methods for Zaltoprofen Cocrystals

Solution-Based Methods

The widespread use of solution-mediated crystallization for the discovery of pharmaceutical cocrystals is attributed to increasing molecular mobility as well as the possibility for heteromolecular interaction [32]. The approaches are concerned with the co-dissolution of the active pharmaceutical ingredient (API) and coformer in a suitable solvent system, thereby allowing for intermolecular associations that can later crystallize to give a unique multicomponent lattice.

Slow solvent evaporation is often used for preliminary screening because the gradual supersaturation of the solution encourages controlled nucleation and also orderly growth of the crystals [33]. For zaltoprofen-type molecules that contain a carboxylic acid group that can create strong hydrogen-bond interactions, this process

can develop sufficiently stable heteromolecular assemblies with appropriate coformers. Nevertheless, crystallization processes rely heavily on solvent polarity, concentration and evaporation rate. Small alterations can lead to the emergence of a cocrystal phase or alternatively, to the recrystallization of each separate component [34].

Slurry conversion is one alternative way to determine thermodynamically stable solids. This means that the API and coformer are dispersed in an appropriate solvent that enables partial solubility so that dissolution–reprecipitation can endlessly occur. Eventually, with time, the dynamic equilibrium can cause conversion to a more stable multicomponent crystal [35]. As slurry methods favor the thermodynamic form, kinetically accessible cocrystal forms may remain unnoticed.

In antisolvent crystallization, the addition of a poorly miscible solvent is made at a sufficiently rapid rate to decrease solubility and create supersaturation, thereby inducing nucleation of the multicomponent phase [36].

While this method can facilitate rapid cocrystal formation, the quick nucleation achieved often results in the generation of small or poorly ordered cocrystals, which can complicate structural characterization and downstream processing [37].

In conclusion, control of crystallization parameters in solvent-based methods is useful for scalability and reproducibility and is especially useful for cocrystal discovery and structural characterization.

Solid-State Methods

Cocrystallization driven by mechanically induced intermolecular interactions is termed a solid-state method. These processes occur in the absence of bulk solvent. The crystal lattice disruption of starting materials and their heteromolecular assembly can be achieved by mechanical activation [38].

Neat grinding is the simplest mechanochemical method, in which mechanical force increases contact between the API and coformer and allows molecular rearrangement that may give rise to a new crystalline phase. Nonetheless, the process does not always complete, and grinding can yield a mixture of amorphous intermediates or physical mixtures requiring careful structural characterization [39].

A small amount of liquid can improve the efficiency of mechanochemical synthesis, and this is done by means of liquid-assisted grinding (LAG). The presence of minute levels of solvent increases molecular mobility and enables enhanced intermolecular interactions, thereby accelerating cocrystallization [40]. Due to the efficiency and low amount of solvent used in the LAG method, it has become widely used for the rapid screening of potential cocrystal systems.

Scale-up to industrial manufacture remains challenging despite mechanochemical methods being attractive from the viewpoint of green chemistry in terms of their low solvent usage and rapid processing. The resultant crystal phase and reproducibility can vary through differences in milling intensity, energy transmission and apparatus arrangement [41].

4. 3 Emerging Techniques

Recent developments in the field of pharmaceutical processing have produced technologies able to join cocrystal formation and scale-up manufacture.

With the help of hot-melt extrusion (HME), mixtures of the API and coformer are subjected to heat and shear in continuous processing [42]. During extrusion, these conditions promote intimate mixing of the molecules of the compound. HME provides distinct advantages for industrial production, including running continuously and integrating into the downstream formulation. However, the applicability of HME stems from the thermal stability of the components.

Another promising approach is spray drying in which the solution containing the API and coformer is sprayed into small droplets and dried rapidly. Swifter solvent removal can lead to a reorganization of the molecules that crystallize as multicomponent phases [43]. Nevertheless, high evaporation rates can produce metastable or amorphous intermediates which need more structural verification.

Technologies involving a supercritical fluid (especially involving CO2) have also been used for producing cocrystals. Supercritical fluids possess the ability to switch their solvent properties [44]. Thus, these systems utilize supercritical fluids to enhance nucleation and particle formation kinetics. Over time, good use of solvent reduction and particle engineering should bring about a new technological change; however, they are complex processes [45]. Further, these processes require specifically designed sophisticated equipment which limits their use.

Comparative Benefits and Scalability

Each preparation technique has its advantages based on the development stage. While solution-based approaches afford well-defined crystals suitable for structural studies, a major limitation for scaling up their use is the solvent and crystallization conditions [46] . Various mechanochemical approaches can screen cocrystals quickly and environmentally friendly . However, maintaining the same crystal phase during scale-up processes can be problematic.

New processing technologies like hot-melt extrusion and spray drying offer significant promise for the cocrystal commercialization through integrated solid-state transformation and particle engineering [47]. Success can be ensured by a careful balance between thermal stability, crystallization kinetics, and phase reproducibility(Table 2).

The preparation method for zaltoprofen systems depends on the stability of the multicomponent lattice; reproducibility of the crystallization pathways; suitability for pharmaceutical scale-up [48].

Table 2: Translational Feasibility of Zaltoprofen Production Methods [32–48]

Technique	**Readiness Level**	**Environmental Impact**	**Key Operational Feature**	Main Scale-Up Challenge	Reference
Mechanochemical (LAG)	Bench-scale	Excellent (Green)	Energy transfer & milling	Limited reproducibility across batches.	38–41
Solution Evaporation	Exploratory	Poor (High solvent)	Solvation & nucleation	Kinetics difficult to control at scale.	33–37
Hot-Melt Extrusion	Commercial-ready	Excellent (Solvent-free)	Thermal & shear processing	Restricted to heat-stable APIs.	42
Spray Drying	Commercial-ready	Moderate	Particle engineering	Risk of forming unstable amorphous solids.	43
Supercritical CO_2	Next-generation	Superior	Precision nucleation	High capital investment and equipment complexity.	44–45

5. Characterization of Zaltoprofen Cocrystals

5. 1 Spectroscopic Techniques

The study of cocrystals through spectroscopic techniques at molecular level. FTIR enables the identification of changes in the vibrational bands associated with functional groups such as those of zaltoprofen carboxylic acid, suggesting a new hydrogen-bonding network [49].

The use of Raman spectroscopy reveals molecular conformation and lattice packing, which could be useful to identify solid-state heterogeneity or phase transformation. Solid-state NMR (SSNMR) can yield a wealth of high-resolution information on intermolecular proximities that provides strong evidence for heteromolecular interactions [50]. Even though these methods provide insight into the mechanism of interaction, cocrystal proof is confirmation through structure.

Thermal Analysis

Thermal methods can provide important information about phase behaviour, stability and energy properties. Differential scanning calorimetry (DSC) is able to detect new endotherms (peaks) at melting temperature which indicates that there are new crystalline phases in the sample [51]. This means that DSC cannot identify cocrystals from eutectics by itself but rather indicates differentiated phases. Thermogravimetric analysis (TGA) confirms the nonexistence of a lattice solvate. Therefore the alleged cocrystals cannot be some kind of solvate. Hot-stage microscopy (HSM) involves a technique that entrains melting, recrystallization and other phase transitions. Heterogeneous nucleation forms essential crystal formations for chemical and metallurgical industries [52]. The given methods together check the thermal robustness and pharmaceutical suitability

Diffraction-Based Strategies

The methods of diffraction provide unquestionable proof of structure The X-ray powder diffraction is very useful in knowing the new crystalline phases by observing their distinct peak patterns and quickly estimating phase purity. Using SCXRD, we can determine the precise molecular arrangements and observe the hydrogen bonding networks directly. SCXRD information helps to understand how the coformers affect the lattice packing and physico-chemical properties. [53] Diffraction analysis is considered the benchmark method for confirming cocrystal structure.

Microscopic and Particle-Size Analysis

The morphology, surface characteristics, and particle variability revealed by microscopy influence dissolution, flow, and compaction. SEM demonstrates changes in habits suggestive of changes in the pathway of nucleation and growth, while optical microscopy shows particle size and laser diffraction shows particle aggregation [54]. Although these methods can shed light on what happens during the manufacturing of the material and processing behaviour, however, they do not independently verify that a cocrystal has been formed.

Other Physicochemical Properties

The inclusion of cocrystals modifies key characteristics impacting their relevance in pharmaceuticals. Lattice stability can be weakened by moisture sensitivity, causing phase conversion or degradation. Polymorphic transformations can influence stability, solubility, and mechanical properties, requiring appropriate screening [55]. In regards to tablet formulation, mechanical properties such as compressibility and deformation must be taken into consideration(Table 3). The environmental stability studies of cocrystal at different temperatures and humidity ensure the robustness of the cocrystal and shows the benefits of modified form over the parent API [56].

Table 3: Hierarchical Characterization Strategy for Zaltoprofen Cocrystals [49–56]

Analytical Technique	Evidence Strength	Critical Insight	Role in Validation	Reference
SCXRD	Definitive	Full 3D hydrogen-bond network mapping	Confirms absolute crystal structure.	53
PXRD	Primary	Phase fingerprinting	Ensures homogeneity and purity across the batch.	53
FTIR	Supportive	Vibrational shifts	Detects subtle changes in local chemical environments.	49
DSC	Supportive	Thermal signature	Identifies unique melting points, confirming distinct phase.	51
TGA	Exclusionary	Residual solvent analysis	Confirms cocrystal formation versus solvates.	50–52

6. Impact on Solubility and Dissolution Behavior

Enhancement of Equilibrium Solubility

Cocrystal engineering is being increasingly studied as a solid-state approach to enhance the apparent solubility of poorly water-soluble drugs through modification of intermolecular arrangement in the crystal lattice, while the chemical structure of the active pharmaceutical ingredient (API) remains unchanged [57]. Low aqueous solubility of zaltoprofen is due to strong crystal packing interactions with a predominance of hydrophobic aromatic moiety. An appropriate coformer can reorganize these interactions and form a new multicomponent lattice with different thermodynamic properties.

In most cases, zaltoprofen hydrogen bonding occurs with the carboxylic acid group of zaltoprofen and different types of complementary functional groups of the coformer. These heteromolecular interactions replace some of the homomolecular interactions present in the native drug crystal. The structural reorganization might weaken the coupling of the lattice, and allow for a more favourable interaction with the solvent which might enhance the apparent equilibrium solubility [58]. However, not all cocrystals possess such improvement as inherent property. The solubility of a cocrystal is ultimately governed by the relative thermodynamic stability of the multicomponent lattice. Highly stable cocrystals may essentially show little deviation from the solubility of the parent drug [59].

The dissolution behavior may also be influenced by the solubility properties of the coformer, affecting the equilibrium of dissolution and the transient increase in the concentration of the drug in the solution. Nonetheless, the effect will vary immensely based on the pH, buffer, values, and ionic strength which would require a thorough assessment under relevant conditions [60]. As a result, not all multicomponent systems provide a meaningful thermodynamic benefit over the original API. So, the solubility enhancement through cocrystallization should be scrutinized(Table 4).

Table 4: Optimizing Bioavailability: Solubility and Dissolution Kinetics [57–69]

Solid-State Form	Solubility Profile	Release Mechanism	Patient-Centric Impact	Reference(s)
Native Zaltoprofen	Limited	Lattice-restricted dissolution	Slow onset and variable plasma absorption.	57–60
Rationally Designed Cocrystal	Substantially Improved	Rapid solvent infiltration	Accelerated therapeutic effect and enhanced bioavailability.	61–66
Amorphous Form	Maximum but unstable	High-energy burst release	Risk of precipitation; inconsistent drug levels.	67–69

Dissolution Rate Profiles

For many drugs characterised by dissolution-limited absorption, it is often the dissolution kinetics that are more relevant than the equilibrium solubility. Cocrystallization affects dissolution behavior through the alteration of crystal packing, surface energy and wettability [61]. The aforementioned factors govern the solid surface and dissolution medium interaction.

The intrinsic dissolution rate (IDR) is a methodological tool to compare the dissolution profile of two solid forms at a constant surface area. The IDR values of Zaltoprofen cocrystals may be higher because the weakening of lattice inter-chain forces or improvement of surface wettability favours fast penetration of the solvent in the cocrystal surfaces.

Nonetheless, when interpreting this correlation, one should be cautious about the dissolution data, as crystal morphology, orientation and surface roughness will also influence the measured dissolution rates.

Although not currently recognized by regulatory authorities, comparative dissolution testing using standard USP apparatus provides valuable insight into drug release behavior under hydrodynamic conditions relevant to oral dosage forms. Multiple cocrystal systems exhibit faster initial dissolution than that of the pure drug. Nonetheless, such an advantage may be lost if the cocrystal undergoes solution-mediated phase transformation by precipitating the less soluble parent drug on dissolution. Consequently, to assess the improvement in dissolution meaningfully, the release kinetics and phase stability in the dissolution environment must be evaluated simultaneously [62].

Case Studies of Zaltoprofen Cocrystals.

A small number of studies have investigated the cocrystallization of zaltoprofen with pharmaceutically acceptable coformers to improve dissolution performance. Of the reported systems, those formed from nicotinamide and 4,4′-bipyridine are of particular interest due to their strong hydrogen-bond accepting ability [63].

Zaltoprofen's N-oxides and N-oxides of aromatic amines can be formed by photochemistry in a polymeric matrix. Often, the systems are generally prepared through solution crystallization/mechanochemical approaches and characterized by spectroscopic/diffraction techniques. An analysis of the structure reveals the formation of hydrogen-bonded heterosynthons between the carboxylic acid group of zaltoprofen and the amide functionality of nicotinamide [64]. As a result, a modified crystal packing arrangement occurs. This change can lead to a different dissolution behavior but the degree of improvement will strongly depend on the thermodynamic stability of the resulting lattice.

The potential for cocrystallization with 4,4′-bipyridine has also been explored in which the acidic functionality of zaltoprofen is accepted by the hydrogen bond acceptors of pyridine nitrogen atoms. As a result of supramolecular assembly, alteration of intermolecular packing occurs along with the decrease in interaction with aqueous medium. However, improved dissolution is not just due to heteromolecular bonding. There is a practical advantage of cocrystal which gets determined by the coformer solubility, stability of the lattice as well as dissolution phase transformation rate [65].

The combination of these studies shows that in the case of zaltoprofen, cocrystallization can influence dissolution behaviour. However, it will not work with any coformer. Therefore, careful selection and evaluation with respect to thermodynamic and kinetic properties are vital [66].

Getting to Know Solubility and Dissolution.

The reorganization of the intermolecular interactions within the crystal lattice mainly gives rise to improved dissolution performance of pharmaceutical cocrystals. In crystalline form, zaltoprofen is characterized by dense molecular packing and strong drug-drug interactions which results in a stable lattice. The properties of zaltoprofen crystalline lattice restrict solvent access and slow the dissolution of the drug. When a coformer is included to this arrangement, it disrupts the order and results in a heteromolecular crystal that has different cohesive forces and surface properties.

The formation of these structures is typically driven by hydrogen bonding between the carboxylic acid group of zaltoprofen and complementary functional groups in the coformer [67]. Changes in intermolecular interaction result in more efficient packing of solute molecules in the crystal and less disruption energy required for dissolution. Moreover, having a more hydrophilic coformer enhances the surface wettability, which facilitates the faster transfer rate between the solid phase and the medium.

Another reason improved dissolution may occur is the possibility of supersaturated solution formation during cocrystal dissolution. If the coformer dissolves faster than the drug, concentrations of drug may temporarily increase [68]. Nonetheless, this condition can destabilize on its own and subsequent reprecipitation of the parent drug can occur when the cocrystal reverts back to a thermodynamically stable form. Thus, the efficacy of cocrystal systems is reliant not only on the modification of the lattice but also on the kinetic stability of the supersaturated condition in the dissolution process.

Comparison of pure zaltoprofen and other solid-state forms.

The slow dissolution of crystalline zaltoprofen in aqueous media can be attributed to their stable lattice and low water solubility. The introduction of a coformer through cocrystallization makes changes to packing of the molecule as well as surface contact with solvent.

Numerous cases have shown that zaltoprofen cocrystals can dissolve faster and show a moderate enhancement in apparent solubility as compared to the parent drug [69]. The stability of the crystalline structure and the properties of the coformer greatly influence these improvements. If the phase change of cocrystal during dissolution is fast, the benefits might lose.

Cocrystals provide a compromise between performance enhancement and structural stability when contrasted with other solid-state modification methods. More soluble forms of drugs can be achieved using amorphous systems and solid dispersions. However, most of these formulations are physically unstable, as seen from recrystallization. On the contrary, cocrystals maintain the well-defined crystalline architecture while permitting the fine-tuning of drug characteristics via supramolecular plotting. The advantage, therefore, lies in better dissolution behaviour and solid state stability(Figure 3).

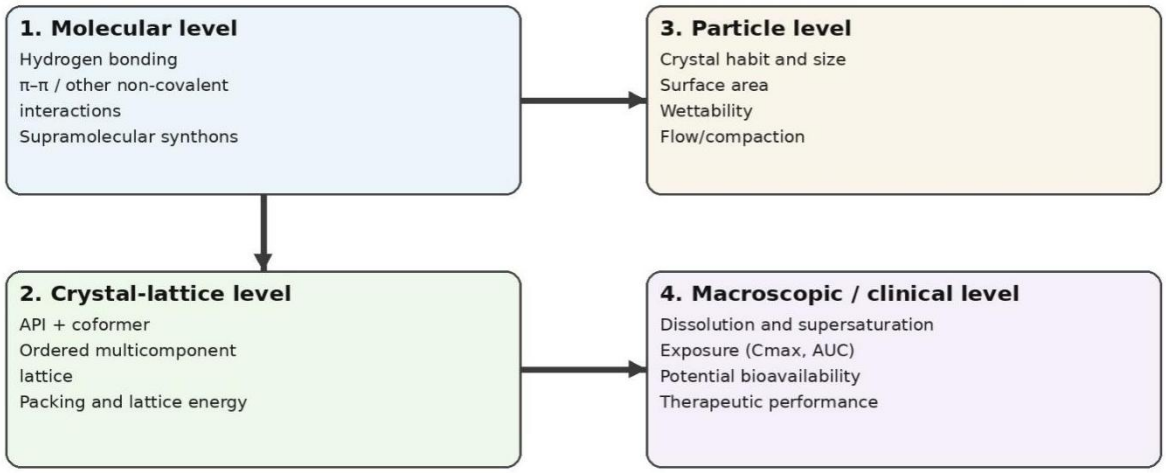

Figure 3. Conceptual dissolution landscape showing competition between transient supersaturation and solution-mediated phase reversion during cocrystal dissolution. Schematic redrawn by the authors based on published cocrystal dissolution and phase-transformation concepts.[61,62,68,71]

7. Stability and In Vitro/In Vivo Performance

Stability of a Drug Product

Pharmaceutical cocrystals can be marketed for a long time provided they retain their structural and chemical integrity after storage. Due to the fact that cocrystals are held by non-covalent attractions rather than attachment with covalent bonding, they are sensitive to changing environmental conditions like temperature, humidity, mechanical stress, etc [70].

One of the most commonly used accelerated stability testing methods for assessing cocrystal stability over time is carried out under controlled temperature and humidity conditions. The exposure to moisture is important as water will disrupt the intermolecular forces that hold the lattice together. It may result in partial dissolution of the cocrystal or the conversion to the original drug crystal particularly if the parent API is a more thermodynamically stable form.Photostability should also be considered, especially due to the degradation of aromatic molecules due to light. As a cocrystal has more than one molecular component in the structure, the degradation of either the API or the coformer destabilizes the entire crystal. Therefore, comprehensive stability studies should consider both the chemical degradation pathways and the potential solid-state phase transformations as these will affect the credibility of the cocrystal [71].

In Vitro Dissolution-Permeation Relationships

To understand the potential therapeutic benefit of cocrystals, one has to consider how the dissolution behaviour may affect membrane transport. Dissolution studies determine the rate at which the drug enters into solution while permeation studies estimate the ability of the drug in solution to cross biological membranes or membrane models.

For drugs like zaltoprofen, which are poorly soluble, it is this step that often gets to control the amount of drug available for absorption. The enhancement of solubility of the drug in solution improves the therapeutic activity of the drug as well as reduces the toxicity. Instead, improved dissolution does not mean better absorption [72].

One key factor is how stable the dissolved drug in solution is. If a drug quickly precipitates or becomes a less soluble crystalline form after being dissolved, the actual concentration available for permeation may drop. As such, studies investigating dissolution–permeation in combination illustrate the dynamic interplay between drug release, supersaturation, precipitation, and offer a better prediction of potential in vivo behavior [73].

Implications of Pharmacokinetics.

The solubility and dissolution properties affect the absorption pattern of an orally administered drug, which subsequently alters the pharmacokinetic parameters. In case of dissolution-limited absorption drugs, an increase in their dissolution may increase the fraction of the compound absorbed.

In theory, quicker drug release will lead to an earlier peak plasma concentration (Tmax) whilst a higher concentration of dissolved drug will increase the maximum plasma concentration (Cmax) and the overall systemic exposure [74]. However, the pharmacokinetic advantages are not automatically translated from the in vitro enhancement.

The final concentration of the drug in the systemic circulation can be influenced by a variety of physiological factors, including the permeability of the intestine, metabolism by enzymes and phase changes during dissolution of the cocrystal. As a result, the researchers warn that the modest improvements seen in dissolution test in the laboratory should not be overly interpreted but rather confirmed by in vivo pharmacokinetic studies suitably designed.

Difficulties and constraints.

Even though pharmaceutical co-crystals can efficiently modify drug properties yet their actual incorporation is

hampered by various issues. The solid-state stability is one major limitation of the multicomponent lattice, which is held together by weak intermolecular interaction. Disruption of the orderly arrangement due to environmental conditions like humidity, temperature variations or mechanical forces will induce reversion to parent drug or other crystalline phases. Such changes may nullify the dissolution advantages of the cocrystal formation(Figure 4) [75].

Another area of concern includes phase transformation during the dissolution. In an aqueous medium, a cocrystal's disassociation may lead the active drug to crystallize into its thermodynamically stable form, if supersaturation cannot be achieved. As a result, a lower concentration of drug may be maintained in solution, which may limit the expected enhancement in dissolution behavior.

Regulatory and analytical considerations are complications to development. In order to recognize a co-crystal, it has to be distinguished from the polymorph, solvate or simple physical mixture V[76]. This requires extensive structural characterization and reliable analytical techniques are required. It is difficult to obtain uniform phase purity in batches of manufacture. The effective solid state characterization, stability studies and stringent process controls play an important role in the successful scale-up of cocrystal technology.

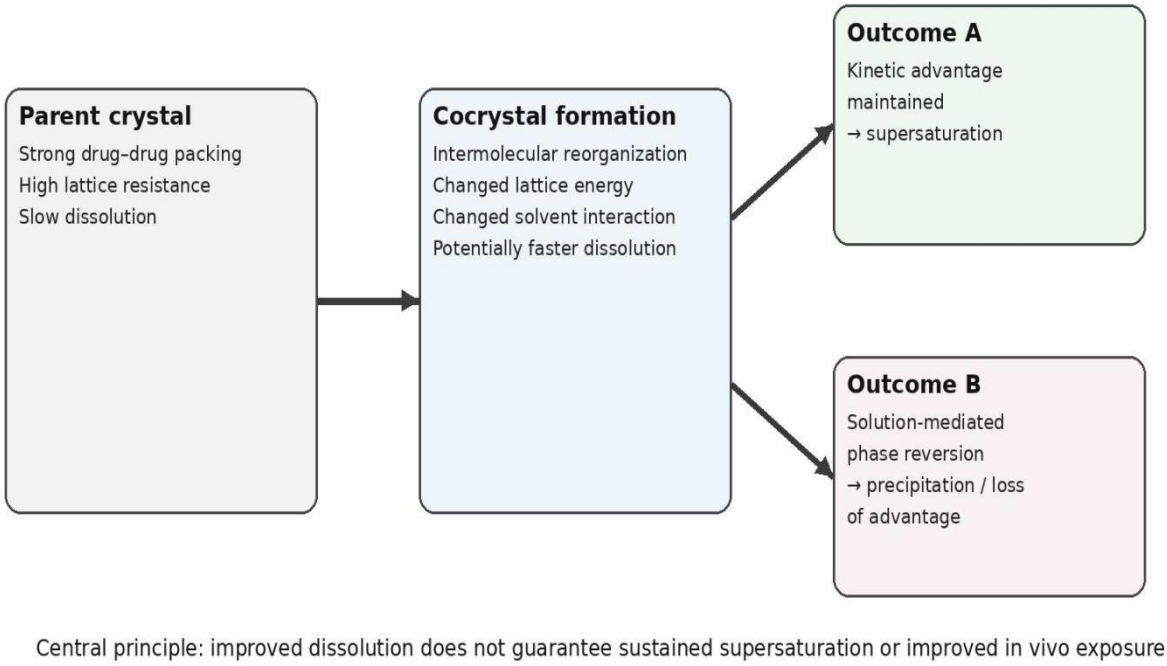

Figure 4. Thermodynamic–kinetic relationship in cocrystal dissolution, illustrating how lattice reorganization may improve dissolution but can lead either to sustained supersaturation or solution-mediated phase reversion. Schematic redrawn by the authors based on published cocrystal stability and dissolution literature.[57–60,70–71]

8. Future Perspectives and Challenges

It is not difficult to produce many pharmaceutical co-crystals in the laboratory. However, making the systems compatible with the industry is challenging. Commonly undertaken methods, like small-scale crystallization in solvent or hand crushing, fail to work on a large scale. I'm sorry, but Laboratory-scale methods may not translate directly to industrial manufacture [77].

It symbolizes yet another hurdle. Variation in solvent composition, temperature, or mixing conditions of a solution affects the crystallization pathway which induces emergence of different phase forms or fails to induce cocrystal formation. As a result, large-scale production necessitates a well-defined set of process parameters, the implementation of monitoring strategies, and quality control measures to ensure phase purity is consistent.For cocrystals to be therapeutically effective, they must retain stability throughout formulation and dosage-form manufacturing. Milling, granulation and compression are mechanical operations that can induce stress that alter the crystal structure. If phase conversion occurs during the processes, the benefits of cocrystal may get lost [78].

In this regard, excipient compatibility, manufacturing conditions and environmental factors that could affect stability of the multicomponent lattice must be given due consideration when designing the formulations. Furthermore, dissolution behaviour of isolated cocrystals may also be altered upon incorporation into a final dosage form as a result of interactions with excipients or changes in the micro-environment [79].

Most of the current research is focused on an oral solid dosage form but further investigations are required to know the behaviour of cocrystals in other delivery systems. Development in this regard depends on procedures assuring structural reliability,

manufacturability as well as predictability of drug release from the dosage form.Pharmaceutical cocrystals refer to crystalline solids comprising an active pharmaceutical ingredient (API) and one or more coformers. The intellectual property protection of these compounds is complex as they lie between polymorphs, salts, and new chemical entities.

A patent must be novel, non-obvious, and useful. The novelty can depend on the particular crystal lattice, while the non-obviousness is difficult because selecting a coformer to being routine can be considered predictable in a free contextual interpretation. When improvements in physicochemical properties lead to clear formulation or therapeutic advantages, utility is enhanced [80].

The combination of composition claims, process claims, and functional claims constitutes effective protection. The strongest composition claims may be the most defensible, process claims can add value when they create new forms, and functional claims must show tangible benefits. Coformer-class claims that are too broad are often contested. A successful example is the sacubitril/valsartan cocrystal present in Entresto® patent, while many carbamazepine cocrystal patents encountered obviousness issues.

Research on cocrystals is gradually stepping into the realm of multi-component cocrystals where the solubility, stability and combination therapy effects can be optimized. However, issues relating to reproducibility and the challenges posed by thermodynamic stability will need to be effectively addressed. Ionic cocrystals exhibit enhanced solubility owing to regulatory concerns and stability issues [81].

Although AI and computational tools assist in the prediction of coformers, they have not yet been a totally reliable guide – virtually all the candidates suggested by AI require experimental testing. Although mechanical and chemical discovery processes have expedited conception, fabrication has got tricky.

There is a growing interest in utilizing sustainable methodologies including solvent-minimizing and green crystallization techniques, yet only a handful of cocrystals have been commercialized. In the end, achieving progress will depend on balancing innovation with reproducibility, evidence of benefit, and sound IP and regulatory strategy [82].

Table 5: Risk Anticipation and Mitigation for Real-World Deployment [70–82]

Potential Risk	Root Cause	Consequence on Product Quality	Mitigation Strategy	Reference
Phase Reversion	Moisture exposure	Reversion to poorly soluble form	Moisture-resistant packaging and controlled storage.	70–71
Precipitation	Supersaturation instability	Loss of solubility advantage	Use of polymeric inhibitors to delay recrystallization.	68,71
Mechanical Stress	Tableting/Milling	Crystal deformation or amorphization	Compatibility studies with excipients; stress optimization.	78–79
Regulatory Delays	Formulation complexity	Extended approval timeline	Develop comprehensive analytical and documentation standards.	76,80–82

9. Conclusion

The BCS Class II agent zaltoprofen (ZLT) is poorly soluble; thus, the formation of pharmaceutical cocrystals (PCCs) is potentially useful. Cocrystallization is a process of modification of the physicochemical properties of the active ingredient of a drug without modifying the chemical structure of the active ingredient through an arrangement of a multicomponent lattice by non-covalent interaction that includes hydrogen bonding to the drug carboxylic acid moiety.

This approach may offer an advantage over amorphous systems as regards to enhanced dissolution while maintaining the requisite order and stability for pharmaceutical development.

Alteration of crystal packing of zaltoprofen described in this manuscript helps in improving its surface wettability and dissolution kinetics using coformers like nicotinamide and 4,4′-bipyridine. All high energy lattices may not work. If a cocrystal undergoes a solution-mediated phase transformation back to a less soluble parent drug after administration, the poor performance may be due more to a lower energy and solubility of the cocrystal than the higher energy lattice. Furthermore, the current reliance on categorization of lab-scale mechanochemical screens restrict more rapid industrial translation.

The development of zaltoprofen cocrystals should therefore be guided by both material-design principles and practical pharmaceutical requirements. Future research should shift from trial-and-error screening to predictive computational modelling supported by scalable emerging manufacturing technologies, such as hot-melt extrusion. The cocrystals' usefulness in real life will depend on their ability to remain supersaturated in vivo, and whether they show real improvement in systemic bioavailability after proper pharmacokinetic validation.

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