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PHARMACEUTICAL COCRYSTALS: MECHANOCHEMICAL AND COMPUTATIONAL METHODS FOR SUPRAMOLECULAR ENGINEERING TO IMPROVE THE SOLUBILITY OF BCS CLASS II/IV APIS AND HERBAL ACTIVES

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ABSTRACT

Pharmaceutical cocrystals use supramolecular synthons to construct non-covalent lattices with GRAS coformers to solve the solubility and bioavailability issues of BCS Class II/IV APIs, including hydrophobic herbal actives. In addition to evaluation by DSC, PXRD, FTIR, Higuchi-Connors solubility (2-14 fold enhancements, e.g., quercetin-caffeine electrospray 14x), dissolution kinetics, and ICH stability studies, this review covers solution-based (solvent evaporation, anti-solvent, cooling, slurry) and solid-state (neat/LAG grinding, melt) synthesis techniques. Despite difficulties such as excipient instability and phase transitions, benefits include green chemistry, IP extension, and better tabletability than salts for neutral APIs; Herbal cocrystals and synthetic APIs are listed in Tables 1-2, which provide cocrystals as a feasible option for rapid/sustained release formulations in contemporary drug delivery.

KEYWORDS: Cocrystal, coformer, API, crystallization, Solubility.

INTRODUCTION

The therapeutic success and industrial manufacturing costs of solid-dosage pharmaceuticals are heavily dictated by the physicochemical attributes of **Active Pharmaceutical Ingredients (APIs)**. Essential parameters, including metabolic stability, gain size, flow characteristics, and moisture sensitivity, play a decisive role in the final performance of the drug.[1] Recent data suggests a trend toward increasingly hydrophobic molecules; currently, 60–70% of new chemical entities are categorized as **BCS Class II or IV**, denoting limited aqueous solubility.[2]

Such hydrophobic tendencies often lead to erratic systemic absorption and diminished bioavailability.[3] Furthermore, the varying pH landscape of the human digestive tract causes these drugs to exhibit inconsistent solubility across different gastrointestinal segments, making it difficult for researchers to establish reliable safety and efficacy benchmarks.[4]

Solubility is defined as the molecular integration of a solute into a solvent to create a uniform, single-phase system.[5] To address low solubility, researchers have utilized several strategies, such as nanocrystal synthesis, lipid-based delivery, and cyclodextrin complexation.[6] While traditional methods like salt formation or solid dispersions are common, they frequently suffer from stability issues or scalability hurdles. In this context, **cocrystal engineering** has emerged as a superior strategy for enhancing solubility while preserving the API's molecular stability.

ADVANTAGES OF COCRYSTALS

i. mproved solubility and dissolution rates for weakly soluble medicines, hence increasing bioavailability.[7]
ii. Improved physical stability, including lower hygroscopicity, tabletability, and mechanical characteristics.[8]
iii. Chemical stability against moisture, heat, and light, with the possibility of flavor masking and lowered toxicity.[9]
iv. Expanded intellectual prIoperty through new solid forms without modifying the API chemically.[10]
v. Green chemistry potential through solvent-free synthesis, which reduces development timeframes and costs.[11]

DISADVANTAGES OF COCRYSTALS

i. During processing or dissolution, the coformer dissociates or is converted to a less soluble parent drug.[12]
ii. Scalability issues arise when moving from laboratory to industrial production, including yield and consistency optimization requirements.
iii. Fixed stoichiometric ratios limit dose flexibility in formulations.
iv. Instability with excipients or in hostile environments such as acids and bases.[13]

Pharmaceutical Cocrystals

Cocrystal technology represents a sophisticated supramolecular solution for modern drug delivery challenges.[14] These are defined as multi-component crystalline materials consisting of an API and one or more stoichiometric co-formers (or another API) held within a shared crystal lattice.[15]

The **U.S. Food and Drug Administration (FDA)** classifies cocrystals as crystalline molecular complexes where the individual components exist in a neutral state, interacting through non-ionic pathways.[16] Unlike traditional salts, which require proton transfer between components, cocrystals are assembled via:

- **Hydrogen bonding**
- **Van der Waals forces**

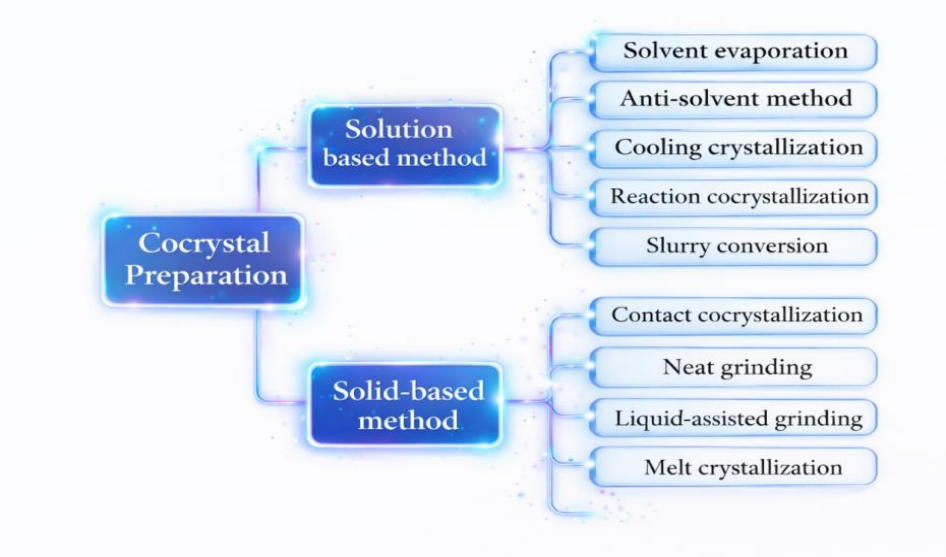
- π–π Stacking **interactions**

At room temperature, these materials remain stable solids, exhibiting unique internal arrangements and crystal habits that distinguish them from their pure constituents. This structural distinctiveness allows developers to manipulate the physical behavior of a drug without modifying its pharmacological core.[17] Cocrystals are especially beneficial for APIs that lack ionizable sites, making them a viable alternative when salt formation is chemically impossible.

By pairing a drug with a suitable co-former, developers can achieve:

- **Superior dissolution rates** and increased saturation solubility.[18]
- **Resilience** against environmental stressors like heat and humidity.
- **Fine-tuned drug release** and pharmacokinetic profiles.[19] Ultimately, the application of cocrystal technology facilitates more robust drug formulations, improving clinical outcomes and patient compliance.

METHODS OF COCRYSTAL FORMATIONS



1. Solution-Based Methodologies

Solution-based techniques synthesize cocrystals within a ternary environment (API, coformer, and solvent) by manipulating the saturation levels and crystallization tracks. These methods are highly versatile and preferred for high-purity material screening.

A. Solvent Evaporation

This technique is primarily used to grow high-purity single crystals for X-ray diffraction. Stoichiometric amounts of API and coformer are dissolved in a solvent with congruent solubility. After initial stirring (approx. 600 rpm for 45 minutes) to ensure uniformity, the solvent is slowly removed at temperatures between 25 and 40°C. This gradual process triggers nucleation and crystal growth.[7]

B. Anti-Solvent Method

Equimolar amounts of API and coformer are dissolved in a concentrated solvent (e.g., methanol) at elevated temperatures. To force rapid supersaturation, this solution is added dropwise to a chilled anti-solvent (0–5°C) under

high-speed agitation (800–1200 rpm). The resulting suspension undergoes Ostwald ripening on ice, often assisted by sonication to refine the crystal habit, followed by filtration and vacuum drying.[20]

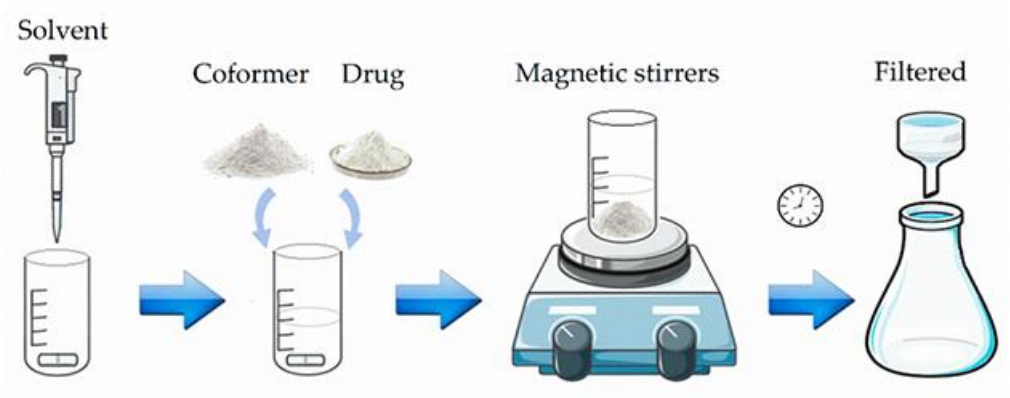
C. Cooling Crystallization

Widely utilized in industrial pharmaceutical manufacturing, this method leverages the temperature sensitivity of solute solubility.

- **Process:** A saturated solution is prepared at high temperatures (50–70°C).
- **Controlled Cooling:** The mixture is cooled gradually (0.1–0.5°C/min) to room temperature.
- **Yield Enhancement:** If nucleation is delayed, seeding with pure cocrystals or further cooling to 5°C is employed to maximize recovery, typically yielding 70–90%.[21]

D. Reaction Cocrystallization

This involves adding the drug in excess of its solubility to a saturated coformer solution. As the drug dissolves, the system reaches a state where the cocrystal phase is the least soluble, leading to its precipitation. The mixture is stirred until the transformation is complete and then filtered.[21]



E. Slurry Conversion

In this approach, the API and coformer are stirred in a solvent in which they have limited solubility, creating a slurry. The transition to a cocrystal occurs through a solid-state mediated process in the liquid medium. The remaining solvent is evaporated to yield crystals suitable for PXRD analysis.[22]

2. Solid-State Methodologies

Solid-based methods are "green" alternatives that utilize mechanical or thermal energy rather than large solvent volumes. These techniques reduce environmental impact and are effective for coformers with poor solubility.[23]

A. Contact Crystallization

This method relies on epitaxial growth and inter-crystal contact within a metastable zone. By agitating a stoichiometric mixture in a minimal hot solvent and cooling slowly, nucleation is induced at the contact points. Real-time monitoring via Raman or ATR-FTIR ensures phase purity during the 1-to 24-hour process.[24]

B. Neat Grinding (Mechanochemistry)

A purely solvent-free method where stoichiometric powders are subjected to high-energy mechanical force. Using a mortar and pestle or a ball mill (20–30 Hz), the shear force breaks existing molecular bonds, allowing for the diffusion and reformation of hydrogen bonds between the API and conformer.[25]

C. Liquid-Assisted Grinding (LAG)

LAG enhances neat grinding by adding a catalytic trace of solvent (~0.1-0.25 μL/mg).

- **Mechanism:** The solvent acts as a lubricant and a localized medium for solvation/desolvation, significantly accelerating reaction kinetics.
- **Advantages:** It provides better polymorphic control and higher crystallinity compared to dry grinding, without the solvent being incorporated into the final crystal lattice.[22]

D. Melt Crystallization

This thermal approach involves heating a stoichiometric blend above its eutectic point (typically 80–160°C) to create a uniform molten phase. After holding the melt to ensure homogeneity, it is cooled at a controlled rate (1–5°C/min). This solidification process results in a bulk cocrystal, which is then pulverized for characterization via DSC or PXRD.[25]

COMPUTATIONAL TOOLS FOR COFORMER SELECTION

While DSC validation is still crucial in hybrid workflows, computational tools for pharmaceutical cocrystal coformer selection, such as CSD-based hydrogen-bond analysis, DFT-D CSP for lattice energy prediction, COSMO-RS for solubility screening, and MEP/HSP/HBP descriptors with QSAR models, enable effective virtual prioritization of GRAS candidates like those from ZINC/PubChem.[26]

Cambridge Structural Database (CSD)

1. Principles of Supramolecular Design in Cocrystallization

The structural integrity of a pharmaceutical cocrystal is dictated by supramolecular synthons—fundamental units of assembly formed through the deliberate association of an Active Pharmaceutical Ingredient (API) and a guest molecule (coformer). Successful synthesis relies on the presence of functional groups that facilitate either homosynthons (bonding between identical molecular species) or heterosynthons (selective bonding between different species).

1.1 The Systematic Four-Tiered Development Path

The evolution from a bulk API to a refined crystalline complex follows a rigorous structural protocol:

- **API Profiling:** The initial phase focuses on identifying a candidate drug molecule with suboptimal properties, such as inadequate aqueous solubility, thermal instability, or poor flowability.
- **Molecular Recognition & Partnering:** This involves identifying coformers that possess chemical groups complementary to the API, ensuring they are capable of establishing robust, non-covalent intermolecular connections.
- **Synthesis & Nucleation:** Various mechanochemical or solution-mediated techniques are applied to trigger the physical assembly and growth of the crystal phase.
- **Characterization & Performance Mapping:** The final product's lattice is scrutinized to confirm that its pharmacological and physical attributes exceed those of the original uncomplexed drug.

2. Informatics and Predictive Tools

The rational engineering of cocrystals is driven by data-centric tools that evaluate molecular compatibility before benchwork begins.

2.1 CSD-Driven Heterosynthon Forecasting

The Cambridge Structural Database (CSD) is utilized to conduct statistical assessments of molecular motifs. By mining data from millions of established structures, scientists can rank potential coformers based on their likelihood of forming stable supramolecular heterosynthons.

Prominent High-Probability Heterosynthons

- **Carboxylic Acid ↔ Amide:** A highly resilient and predictable motif used to bridge acidic APIs with amide-bearing coformers.
- **Carboxylic Acid ↔ Aromatic Nitrogen:** A strategic pairing often employed when the drug contains carboxylic moieties and the guest molecule features pyridine-type rings.[27]

2.2 Thermodynamic Compatibility via Hansen Solubility Parameters (HSP)

Beyond structural motifs, Hansen Solubility Parameters are applied to evaluate the theoretical miscibility of the API and coformer. By calculating the cohesive energy density, HSP ensures that the two components are chemically compatible enough to form a homogeneous solid phase rather than separating into their original parts.[28]

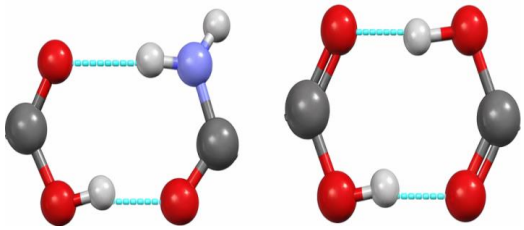
2.3 Synergistic Integration of Parameters

In modern research, the synergy between supramolecular synthons, HSP thermodynamics, and CSD informatics represents the gold standard for coformer selection. This review integrates these parameters, demonstrating how hydrogen bonding propensities and solubility data correlate to streamline the discovery of optimized pharmaceutical forms.

- **Supramolecular Synthon Approach**

Pharmaceutical cocrystals are created in the realm of crystal engineering by optimizing an Active Pharmaceutical Ingredient (API) using supramolecular chemistry concepts while retaining its core molecular structure. This design philosophy sees crystalline solids as the result of molecular self-assembly, which is fueled by a network of non-covalent connections. The Role of Non-Covalent Forces Synthesis is based on modulating several important intermolecular interactions. Hydrogen bonds, π–π stacking, Van der Waals Forces, electrostatic and hydrophobic effects. Supramolecular Synthons The main structural units of these supermolecules are known as supramolecular synthons.

These recurrent patterns of interaction are classified according to the functional groups involved.



a **b**

a. **Heterosynthons:** Diverse but chemically compatible functions.
b. **Homosynthons:** Formed by the connection of identical, self-complementary functional groups, such as carboxylic acid dimers or amide dimers.

Common examples are carboxylic acid-amide interactions.

Carboxylic acid–pyridine motifs.

Alcohol/ether combinations.Structural robustness.

According to research, heterosynthons are typically more structurally stable than homosynthons. For example, the acid-amide heterosynthon is energetically preferable to the synthesis of individual carboxylic acid or amide homodimers, making it an effective tool for guided crystal design.[29]

B. COSMO-RS Model

COSMO-RS is a sophisticated computational framework that calculates the activity coefficients (γ) of compounds in a chemical mixture using statistical thermodynamics and quantum mechanics. A molecule in a perfect dielectric medium is surrounded by a tessellated boundary called a σ-surface (sigma surface), which is created by the model. Fundamental Functional Mechanism Surface Charge Density: Screened charge densities are mapped across molecular sections by the σ-surface. Energy Prediction: The model computes excess Gibbs energies and activity coefficients using pairwise interactions between these surface segments. Geometric Sensitivity: Because changes in molecule geometry (conformers) impact the sigma surface, the selected conformer has a direct influence on the activity coefficient estimates.Technical Parameters and Optimization.In some research applications, the program TURBOMOLE is used for geometry optimization using its COSMO-BP-TZVPD-FINE template. This technique uses Density Functional Theory (DFT) with numerous customized parameters.

Functional: BP-86.

Basis Set: Triple -ζ polarized with diffuse functions (def2-TZVPD).

Parameterization: BP_TZVPD_FINE_21, which is integrated with the COSMOtherm software package. Conformer Weighting COSMO-RS has the capacity to combine several molecular conformers into a single computation. Using a Boltzmann distribution, the model calculates the influence of each conformer j in a solvent S. This weighting is dependent on the conformer's particular free energy, computed as ($E_j^{COSMO} + \mu_j^S$).

$$\pi_j^s = \frac{w_j \exp\left(\frac{E_j^{\mathrm{COSMO}} + \mu_j^s}{kT}\right)}{\sum_m w_m \exp\left(\frac{E_m^{\mathrm{COSMO}} + \mu_m^s}{kT}\right)}$$

In this equation, πj is the proportion of molecules identified as conformer j, and wj is a weight prefactor that determines its state degeneracy (or multiplicity).[30]

C. DFT-D CSP

In the field of crystal engineering, **Density Functional Theory (DFT)** is a fundamental tool for performing quantum chemical assessments of crystal structures, their energetic profiles, and vibrational characteristics. This computational

approach provides critical insights into how molecules pack and how their physicochemical behaviors, such as solubility, are determined.

1. Crystal Prediction and Examination of Crystal Stability

DFT identifies the most stable crystal forms by calculating the **Gibbs free energy (ΔG)**. Based on the second law of thermodynamics, the polymorph with the lowest value of Δ**G** is considered the most thermodynamically stable.

- **Free Energy Components**: Stability assessments integrate lattice energy and intermolecular interaction energies to determine Delta ΔG.
- Thermodynamic Formula: The relationship is defined by:

$$\Delta G = \Delta H - T\Delta S,$$

where Δ H is the change in enthalpy, ΔT is the temperature in Kelvin, and Δ S is the change in entropy.

- **Standardized Assessment**: These parameters are typically calculated under standard conditions (298 K, 1 atm). A negative ΔG confirms an exothermic or spontaneous process.

2. Crystal Structure and Phase Transitions

By optimizing structures derived from experimental methods like XRD or NMR, DFT validates the most energetically favorable configurations.

- **Periodic DFT (PDFT)**: This technique generates potential crystal structures and screens for stable forms through Gibbs energy calculations.
- **Polymorphic Elucidation**: Subtle differences between crystal forms are analyzed using vibrational spectra and free energy data.
- **Metastable Transitions**: Metastable forms—which possess higher energy due to conformational flexibility—can transition to stable polycrystalline states when energy is applied (e.g., through grinding). This process allows molecules to overcome low-energy barriers to form more stable supramolecular synthons.

3. Co-Crystallization and Reaction Pathways

DFT clarifies the mechanisms behind cocrystal formation by examining changes in electronic structures and hydrogen-bonding motifs. These theoretical models are frequently verified against experimental data from **terahertz (THz-TDS)** and **Raman spectroscopy**.

- **Hydrogen-Bonding Analysis**: Research has demonstrated how specific dimers form through O−H···O hydrogen bonds, such as in the gallic acid and acetamide system.
- **Structural Optimization**: Common computational settings for these models include the **B3LYP functional** and the **6-311++G (d,p)** basis set.
- **Enhanced Stability**: Cocrystals, such as those formed between rifampicin and tromethamine, achieve greater stability through the creation of energy-lowering hydrogen-bond networks.[31]

MULTICOMPONENT CRYSTAL FORMATION

Multicomponent crystals are generated in a variety of processes, including solvent evaporation, slurry conversion, cooling cocrystallization, plain grinding, liquid-assisted grinding, and spray drying (Table 1). The methods were chosen based on the drug and coformer's features.

Table 1: Solubility data of multicomponent crystals of active pharmaceutical ingredients with coformers.

Method	Active Pharmaceutical Ingredient	Coformer	Solubility Enhancement (Fold)	References
Solvent evaporation method	Glibenclamide	Nicotinamide	(>3.5x)	32
		Ascorbic acid	26	33
		Aspartame	20	34
	Ibuprofen	Isonicotinamide/ Nicotinamide	2-4x	35, 36
	Naproxen	Nicotinamide	(>2x)	37
	Indomethacin	Saccharin	(2-5x	38
	Carbamazepine	Succinic acid	~7-10x	39
	Nifedipine	Nicotinamide	4x	40
	Piroxicam	Saccharin	(~3x)	1
	Itraconazole	Glycine, Alanine	3	41
	Flurbiprofen	Nicotinamide	5x	42
	Meloxicam	Succinic acid	12x	43
	Theophylline	Oxalic acid	(~2-3x)	1
	Atorvastatin calcium	Succinic Acid	1.5	5
	Acetazolamide	Proline	3.57	44
	Metaxalone	Nicotinamide	8.6	5
		Salicylamide	4.5	
		4-hydroxybenzoic acid	5	
	Candesartan	Methylparaben	6.94	5
	Xanthohumol	Acetamide	2.6	
		Glutarimide	1.6	
		Nicotinamide	1.4	
		Caffeine	1.3	
	Paliperidone	Benzamide	61	5
		Boric acid	1.48	
		Nicotinamide	18.5	
		p-hydroxybenzoic acid (PHBA)	141	
	Diclofenac potassium	L-Proline	3.56	5
	Aripiprazole	Resveratrol	0.6	45
		Kaempferol	>1	
Slurry conversion	Telmisartan	Gentisic acid Para-aminobenzoic acid 5 Adipic acid	3.7	5
		Maleic acid 4.4	4.4	
		Para-aminobenzoic acid	5	
		Adipic acid	5.4	
Cooling cocrystallization	Etodolac	Glutaric acid	3.61	46
Neat grinding	Mefenamic acid	Nicotinamide	2.56	47
	Zoledronic acid	Nicotinamide	20.12	48
	Carbamazepine	Nicotinamide	1.95	49
	Theophylline	Citric acid:	3	50
Liquid-assisted grinding	Hydrochlorothiazide	Nicotinic acid	2	51
		4-aminobenzoic acid	2.4	52
		Nicotinamide	1.3	
	Caffeine	Citric acid	1.2-1.5	53
		Glutaric acid	~1x	54

	Itraconazole	Aspartic acid	3	55
	Zaltoprofen	nicotinamide	42	56
	Norfloxacin	Nicotinic acid	~2-3x	57
	Ketoconazole	Fumaric acid	75-100x	58
	Olanzapine	2-aminoterephthalic acid	5	5
	Daidzein	Isocotinamide	2.1	59
		Cytosine	1.9	
		Theobromine	1.7	
	Irbesartan	Succinic Acid	1.33	60
		Benzoic Acid	2	61
	Ritonavir	L-tyrosine	11.24	62
	Oxyresveratrol	Citric acid	1.3	63
	Felodipine	imidazole	1.3	64
	Febuxostat	L-pyroglutamic acid	4	65
	Diacerein	nicotinamide	4	66
	Carbamazepine	para-aminosalicylic acid	1.5	67
		tartaric acid	1	68
		benzamide	2-3	69
	Temozolomide	hesperetin	1-1.5	70
	Hydrochlorothiazide	4-dimethylaminopyridine	4	5
		Picolinamide	0.5	
		Phenazine	1.4	
	Gliclazide	succinic acid	2	71
		malic acid	2	
		catechol	2	72
		3,5-dinitrosalicylic acid	6.3	73
		2,6-pyridinedicarboxylic acid	1.8	
		sebacic acid	2.4	74
	Glibenclamide	Succinic acid	3.5	5
		Nicotinic acid	3	
		Hippuric acid	2.2	
		theophylline	1.8	75
	Luteolin	isoniazid	3.2	5
Spray drying	Theophylline	urea	2	76
		saccharin	2	
		nicotinamide	2-3	
	Carbamazepine	nicotinamide	3	77
	Diclofenac	proline	2-3	78

Table 2: Solubility data list of herbal cocrystals along with their coformers and their method of preparation.

Methods	Herbal API	Coformers	Solubility Enhancement (Fold)	References
Flavonoids				
Electrospray	Quercetin	Caffeine	14.0	79
Solvent Evaporation	Quercetin	Nicotinamide	10.0	80
Liquid-Assisted Grinding	Quercetin	Isoniazid	4.5	80
Slurry Method	Quercetin	Theobromine	3.2	81
Solvent Drop Grinding	Hesperidin	L-Arginine	4.5	82
Solvent Evaporation	Hesperidin	Piperine	1.9	80
Solvent Evaporation	Naringenin	Betaine	3.3	
Solvent Evaporation	Naringenin	L-Proline	2.0	

Slurry Conversion	Naringenin	Nicotinamide	2.5	
High-Pressure Homogenization	Baicalein	Nicotinamide	4.2	
Solvent Evaporation	Baicalein	Caffeine	3.1	
Liquid-Assisted Grinding	Baicalein	Proline	2.8	
Liquid-Assisted Grinding	Luteolin	Isoniazid	3.2	
Liquid-Assisted Grinding	Luteolin	Caffeine	2.1	
Liquid-Assisted Grinding	Daidzein	Isonicotinamide	2.1	
Solvent Evaporation	Kaempferol	Nicotinamide	2.8	
Co-melting	Kaempferol	Quercetin	1.5	
Solvent Drop Grinding	Genistein	Caffeine	2.4	
Solvent Evaporation	Apigenin	Caffeine	3.5	
Solvent Evaporation	Myricetin	Caffeine	8.0	
Solvent Evaporation	Myricetin	Proline	12.0	
Slurry Conversion	Myricetin	Nicotinamide	5.5	
Liquid-Assisted Grinding	EGCG	Caffeine	2.0	82
Solvent Evaporation	Rutins	Nicotinamide	2.2	
Polyphenols & Phenolic Acids				
Solvent Evaporation	Curcumin	Isonicotinamide	14.0	83
Liquid-Assisted Grinding	Curcumin	Resorcinol	5.0	84
Slurry Method	Curcumin	Pyrogallol	12.0	
Liquid-Assisted Grinding	Curcumin	L-Carnitine	Improved	82
Solvent Evaporation	Curcumin	Hydroquinone	8.0	84
Reaction Cocrystallization	Resveratrol	Isoniazid	14.0	85
Ultrasound /Microwave	Resveratrol	Piperazine	1.16	82
Solvent Evaporation	Resveratrol	4-Aminobenzamide	3.0	85
Solvent Drop Grinding	Resveratrol	Urea	2.2	80
Slurry Method	Pterostilbene	Piperazine	6.0	
Liquid-Assisted Grinding	Pterostilbene	Glutaric Acid	4.2	84
Solvent Evaporation	Pterostilbene	Caffeine	2.5	
Neat Grinding	Ferulic Acid	Isoniazid	1.8	85
Solvent Evaporation	Ferulic Acid	Nicotinamide	2.4	82
Liquid-Assisted Grinding	Caffeic Acid	Nicotinamide	2.1	80
Solvent Evaporation	Gallic Acid	Caffeine	1.6	
Alkaloids & Others				
Slurry Method	Berberine	Succinic Acid	3.0	
Solvent Evaporation	Berberine	Fumaric Acid	2.5	80
Liquid-Assisted Grinding	Berberine	Oxalic Acid	3.4	
Solvent Evaporation	Piperine	Succinic Acid	1.8	82
Liquid-Assisted Grinding	Piperine	P-coumaric acid	2.2	85
Slurry Conversion	Artemisinin	Hydroquinone	2.0	84
Solvent Evaporation	Artemisinin	Resorcinol	1.5	
Solvent Evaporation	Honokiol	Caffeine	2.8	80
Liquid-Assisted Grinding	Magnolol	Nicotinamide	2.2	80
Solvent Evaporation	Sinapic Acid	Isonicotinamide	1.9	82

EVALUATION OF CO-CRYSTAL

1. Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) is a crucial diagnostic technique used in pharmaceutical research to forecast long-term stability and maximize cocrystal synthesis. By examining 2-5 mg samples of API and coformer mixtures at various molar ratios (such as 1:1, 1:2, and 2:1) across several heating rates, researchers may determine the exact stoichiometry that yields a single, crisp endothermic peak, a feature of high phase purity. By concentrating on the highest onset temperatures and heats of fusion, thermal profiling allows researchers to optimize manufacturing parameters like grinding duration and solvent choice. Additionally, regulated DSC ensures that the final cocrystal is

more than 95% pure by differentiating between reversible and irreversible heat processes. This thorough thermal evaluation effectively connects thermal resistance to enhanced drug solubility and therapeutic efficacy by bridging the gap between lab-scale screening and industrial scale-up.[86]

2. X-ray diffraction (XRD) studies-single crystalline and powder XRD

Pharmaceutical cocrystal development uses powder X-ray diffraction (PXRD) as its main diagnostic method for phase identification and iterative synthesis optimization. Researchers compare diffraction patterns to confirm the emergence of new crystalline lattices, which are usually identified by novel high-intensity reflections or 2θ shifts greater than 0.2°, by methodically varying parameters like solvent volume (5–20 mL/g), milling time (15–90 min), and temperature (RT–60°C). Using Cu Kα radiation with a wavelength of 1.54 Å over a 2θ range of 5–40°, stoichiometric blends—typically 1:1 or 1:2 API: coformer ratios—are created by grinding, slurry conversion, or solution evaporation. Rietveld refinement is then used to show that phase purity surpasses 95%. While Single-Crystal X-ray Diffraction (SXRD) provides conclusive atomic-level structural solutions, the difficulty of generating adequate single crystals often limits its utility, making PXRD the more practical standard for cocrystal screening. In addition to these structural measurements, surface topography and particle morphology are evaluated using Scanning Electron Microscopy (SEM), which scans the sample with high-energy electron beams to more precisely visualize the physical properties of the resulting cocrystals.[87]

3. Fourier transform infrared spectroscopy

Fourier Transform Infrared (FTIR) spectroscopy is an effective analytical tool for determining cocrystal formation and the compatibility of active pharmaceutical ingredients (APIs) and coformers. It examines data throughout the 400-4000 cm^{-1} spectral region to detect variations in vibrational energy peaks that suggest novel intermolecular interactions, namely hydrogen bonding. This method is very beneficial for separating cocrystals from salts; for example, variations in carboxylic acid-related bands assist in elucidating the chemical state of the complex. Absorption spectra of the pure drug, coformer, and their physical mixes are routinely compared to those of the produced cocrystals to demonstrate considerable differences in functional group frequencies. When paired with additional technologies such as DSC or XRD, FTIR gives a strong foundation for screening and validating the effective molecular assembly of medicinal cocrystals.[88]

4. Solubility

The Higuchi and Connors technique is used to evaluate the solubility of pure medicines, physical mixes, and cocrystals by equilibrating the sample in water or a pharmacopoeia-mandated medium. To achieve equilibrium, the mixture is shaken on a rotary shaker for 24 hours at room temperature in a conical flask that is protected from light with aluminum foil if photostability is an issue. Whatman filter paper is then used to clarify the solution, and the resultant aliquots are diluted for quantitative measurement using UV-visible spectrophotometry or HPLC at the proper wavelength.[89]

5. Dissolution study

Dissolution studies are an important diagnostic technique for determining temporal drug release and predicting the in vivo performance of pharmacological formulations, including cocrystals. Using a conventional dissolving device and a medium prescribed by pharmacopoeial procedures, aliquots are collected at predetermined intervals. These samples are

then measured using HPLC or UV-visible spectrophotometry to ensure that the final release profile appropriately reflects the formulation's kinetic behavior and potential bioavailability.[89]

6. Stability study

Stability studies are critical for establishing the shelf life of pharmaceutical goods by evaluating their integrity under a variety of storage circumstances. Drug samples are routinely stored in glass vials and subjected to variations in environmental factors such as humidity, temperature, and light at predetermined intervals. Following exposure, the samples undergo comprehensive characterization—including thermal analysis, drug release profiles, X-ray diffraction (XRD), and Fourier-transform infrared spectroscopy (FTIR)—to identify any physicochemical changes by comparing the post-stability data with the initial baseline results.[89]

APPLICATIONS

Depending on the compound's ionization profile and development objectives, cocrystallization offers targeted advantages over salts by refining medication physicochemical properties without changing the covalent structure of the active medicinal ingredient. Cocrystals with ΔpKa close to zero preserve neutral drug release upon dissolution, preferring situations where kinetic dissolution exceeds steady-state solubility, whereas salts frequently provide greater water solubility through ionization. Improvements in melting behavior, compressibility, dissolving kinetics, chemical resilience, absorption efficiency, and membrane transport are made possible by this method, which is particularly useful for neutral or zwitterionic APIs that are susceptible to salt instability. As demonstrated by commercial solutions that overcome bioavailability barriers for difficult compounds, cocrystals enable tailored formulations like rapid-release tablets or stable dispersions by utilizing safe coformers via hydrogen bonding.

FUTURE PERSPECTIVE

Computational techniques for coformer selection in pharmaceutical cocrystals have revolutionary potential in the future. They can enable fully virtual processes that eliminate the need for significant practical screening of several coformers, saving BCS Class II/IV medications time, resources, and materials. High-throughput ranking of thousands of GRAS-listed coformers using only in silico lattice energy minimization and interaction propensity scoring is made possible by sophisticated physics-based techniques like DFT-D for synthon energy calculations, COSMO-RS for sigma-profile-based miscibility prediction, and crystal structure prediction (CSP) using CSD-derived supramolecular synthons. Emerging AI hybrids like graph neural networks and random forests achieve >80% accuracy in predicting stable cocrystals without any wet-lab validation. Rational design will be standardized by web-integrated platforms like Schrödinger's Materials Science Suite and open-source tools like CrystalExplorer. This will enable direct scale-up to GMP manufacturing, regulatory filings under FDA cocrystal guidance, and patentable solid forms with optimized solubility, bioavailability, and stability for sustained-release formulations.

CONCLUSION

Pharmaceutical cocrystals are a revolutionary approach to drug delivery. They use supramolecular synthons with GRAS coformers to overcome the solubility, bioavailability, and stability issues of hydrophobic herbal actives and BCS Class II/IV APIs through a variety of solution-based and solid-state synthesis techniques, validated by DSC, PXRD, FTIR, Higuchi-Connors solubility assessments (producing 2–14 fold enhancements), dissolution kinetics, and ICH stability studies. Cocrystals' advantages—green chemistry compliance, IP extension, superior tabletability over

salts, and tunable release profiles—position them as a versatile platform for rapid/sustained formulations, bridging computational tools (CSD, DFT-D CSP, COSMO-RS) with industrial scale-up to improve therapeutic efficacy, patient compliance, and commercial viability in contemporary pharmaceutics despite challenges like phase transitions, excipient instability, and scalability.

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