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Review JoPC

Polymer Composite-Assisted Crystal Engineering for Drug Synthesis and Property Control through Solid Solutions and Co-Crystals

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Abstract

The long-standing problem of low aqueous solubility, which affects about 90% of all new drug molecules under development, requires an immediate need for alternative approaches apart from the usual practice of crystallization. Polymer-composite-assisted crystal engineering is a novel technique for overcoming the aforementioned problem. This involves the addition of accepted pharmaceutical polymers, such as HPMC, PVP, PEG, and Eudragit copolymers in a single process, which can promote nucleation, stabilize the metastable crystals, and maintain drug supersaturation in the gastrointestinal tract. A pharmaceutical co-crystal is a multicomponent system where one of the components is an active pharmaceutical ingredient (API) while other components are pharmaceutically acceptable co-formers held by weak intermolecular interactions, including hydrogen bonding, van der Waals forces, and π-π stacking. The co-crystallization strategy proves to be a promising way for enhancing solubility, dissolution, bioavailability, stability, hygroscopicity, and tableting properties of API regardless of the ionization range. With the addition of a polymer into this binary API co-former system, a ternary architecture is created, which demonstrates performance that outperforms both that of the polymer-free co-crystal as well as an amorphous solid dispersion. An increase in solubility by factors of 2-8 over the parent API has been reported in the case of polymer-composite co-crystals, compared to that of the polymer-free co-crystal with an increase by factors of 1.5-5. This review provides a comprehensive overview of the preparation approaches, changes to physicochemical properties, and biomedical applications of the newly emerging class of polymers incorporated within co-crystals and solid solutions. Various solid-state approaches include polymer-assisted liquid-assisted grinding, hot-melt extrusion, and melt crystallization, while liquid state approaches include polymer-directed slurry conversion, reaction co-crystallisation, spray drying, and antisolvent co-precipitation. Changes to the physicochemical properties including physical and chemical stability, hygroscopicity, solubility, dissolution rate, and optical behavior due to incorporation of polymers are reviewed.

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INTRODUCTION

The drug formulation business has a tough task ahead of it; it has to develop formulations for the delivery of active drugs with sufficient solubility, bioavailability, and stability in varying physicochemical conditions during their manufacture and use. The Biopharmaceutical Classification System (BCS) II and IV classes,

suffering from low aqueous solubility and poor dissolution rates, currently account for approximately 40% of already-marketed medications and nearly 90% of new chemical entities in active development [1,2,11]. This solubility crisis has made pharmaceutical crystal engineering one of the most consequential areas of pharmaceutical materials science over the past two decades [3,4].

Co-crystallisation has, in this context, gained significant traction as a relatively novel yet increasingly mature technique for improving solubility, bioavailability, stability, thermal properties, permeability, and tabletability without altering the pharmacological identity of the API [5]. Co-crystals (CCs) are multicomponent systems consisting of an API and a coformer linked together in the crystal lattice by non-covalent interactions principally hydrogen bonds, van der Waals forces, and π–π interactions at a defined stoichiometric ratio [6]. The various solid forms of active pharmaceutical ingredients are illustrated inFig. 2. Co-crystallisation applies broadly across ionisation states (ionisable and non-ionisable APIs alike), and the large combinatorial space of potential coformers provides a realistic prospect of finding a viable co-crystal for virtually any solid API [7,8,12].

Pharmaceutically accepted macromolecular excipients chief among them HPMC, PVP, PEG, and Eudragit copolymers have traditionally been treated as passive binders or matrix agents in final dosage forms. A growing body of evidence now demonstrates that when these polymers are incorporated directly into the co-crystallisation process, they actively direct crystallisation outcomes: they modify nucleation barriers, alter crystal face growth rates, and steer solid-form selectivity in ways that no binary API–coformer system can achieve alone [9,10]. Recent studies have documented these effects for theophylline–benzoic acid co-crystals prepared with HPMC additives [13], for nicotinamide–adipic acid polymorphic selectivity controlled by mechanochemical polymer incorporation [14], and for HPMC-AS/indomethacin–saccharin composites prepared by hot-melt extrusion that simultaneously form co-crystal nanodomains and a supersaturation-stabilising polymer matrix [15].

Another aspect of pharmaceutical crystal engineering is solid solutions, which represent a complementary approach to drug design. Solid solutions are a result of mixing two structurally similar molecules that can occupy the same position in the crystal structure [18], resulting in a mixed crystal with adjustable intermediate properties [21-22]. The inclusion of polymer in the process of solid solution crystallization affects the stoichiometry of the mixed crystal through growth inhibition of one molecule, offering a crucial tool for achieving optimal properties [19]. The co-crystalline solid solution of praziquantel, prepared with polymer-assisted processing, delivered earlier and more consistent oral absorption in rat pharmacokinetic studies compared with the polymer-free form [20], validating clinical relevance.

The present review fills the gap in the literature by placing polymer composites at the centre of the pharmaceutical crystal engineering narrative. We cover all major synthesis routes with explicit attention to polymer effects, map physicochemical property enhancements attributable to polymer composite architecture, discuss mechanistic frameworks for polymer-directed crystallisation, and survey industrial scalability and regulatory considerations.

SYNTHESIS OF CO-CRYSTALS FOR PROPERTY CONTROL OF DRUGS

The synthesis methods for pharmaceutical co-crystals are broadly summarised as solid-based and solution-based approaches. Both categories carry their own advantages and limitations, and both are substantially transformed when a polymer composite strategy is adopted. In solution-based techniques a significant quantity of solvent is required to dissolve the co-crystal components, and solvent selection profoundly alters the intermolecular interactions between coformer and API [23]. Solid-state techniques largely or entirely eliminate solvent demand, and when a polymer is present as a solid additive they combine environmental sustainability with active crystallisation direction. Table 1 below provides a comparative summary of all major synthesis methods.

Table 1. Comparative Summary of Co-Crystal Synthesis Methods and the Role of Polymer Incorporation (Yield, crystallinity, and scale-up ratings are representative literature ranges. CSD = crystal size distribution; PALAG = polymer-assisted liquid-assisted grinding.)

Method	Solvent Need	Typical Yield (%)	Crystallinity	Scale-up Ease	Polymer Role
Neat Grinding	None	59–75	Moderate	Good	Nucleation director; moisture catalyst
Liquid-Assisted Grinding (LAG)	Catalytic	80–92	High	Good	PALAG: viscosity control; polymorph selectivity
Hot-Melt Extrusion	None	88–96	Moderate–High	Excellent	Matrix former + in-situ co-crystal formation
Melt Crystallisation	None	75–88	High	Moderate	Slows kinetics; suppresses competing phases
Slurry Conversion	Moderate	88–95	High	Good	Suppresses competitive monohydrate nucleation
Reaction Co-cryst.	Moderate	82–92	High	Good	Broadens co-crystal stability pH window
Cooling Crystallisation	High	85–92	High	Excellent	Narrows CSD; adsorbs onto fast-growing faces
Spray Drying	High	80–90	Moderate	Good	Simultaneous encapsulation + co-crystal formation
Solvent Evaporation	High	70–85	Very High	Poor	Surface coating improves compressibility
Antisolvent	Moderate	80–92	High	Good	Co-precipitation; particle-size reduction

Solid-Based Co-Crystal Methods

Methods that involve solid-state crystallisation have been found to be effective, environmentally friendly, and suitable for continuous processing, since they do not involve any solvent at all or only a minimum amount of it. If polymers are added to the process in a solid state before any form of grinding or melting, then these crystallisation methods get yet another level of control over polymorphs and yield through the polymer [24].

Melting Crystallisation

Melt crystallization represents another eco-friendly technique for producing drug co-crystals without using solvents [32]. However, it is critical to evaluate the thermal stability of the API and coformer prior to this method [33]. Melatonin-pimelic acid co-crystals were prepared via melt crystallization, as described by Yan *et al*. [33], where the molten solution produced co-crystals on cooling at a temperature range of 50–70°C. Rodrĭguez-Hornedo *et al*. [34] identified two distinct crystallisation pathways for the carbamazepine–nicotinamide co-crystal from the melt: (1) a metastable co-crystal phase nucleated first at a moderate heating rate of 0.05°C/h and subsequently converted to the stable form; (2) at a faster rate of 0.167°C/h, the individual components crystallised separately before combining. When PVP or PEG is incorporated into the melt, the resulting higher viscosity slows crystallisation kinetics, providing longer windows for thermodynamically driven co-crystal nucleation and effectively suppressing separate component crystallisation [15,25].

Liquid Grinding

Liquid-assisted grinding (LAG) consistently produces co-crystal products with higher yields and crystallinity than neat grinding, and is well-suited to rapid co-crystal screening regardless of starting material solubility [26,50]. Adding a small liquid quantity enhances molecular diffusion and accelerates co-crystal nucleation. When a polymer is dissolved in the grinding liquid creating the polymer-assisted liquid-assisted grinding (PALAG) approach the resulting viscosity increase extends the lifetime of the amorphous intermediate phase, providing a longer window for thermodynamically favoured co-crystal nucleation [16].

Fischer *et al*. [36] showed that solvent characteristics in LAG governed the polymorphic outcome of 1:1 caffeine–anthranilic acid co-crystals: Form I was obtained with most solvents, while Form II appeared only in fluids with high carbonyl or nitrile dipole moments. Germann *et al*. [37] reported a previously unstudied influence of milling assembly on mechanochemical polymorph interconversion between stable Form I (7.5 kJ/mol) and metastable Form II (10.2 kJ/mol) of nicotinamide–adipic acid co-crystals during LAG. In the presence of polymeric grinding additives, selectivity for the thermodynamically preferred form can be enhanced by approximately one to two orders of magnitude in nucleation rate ratio [14,37].

Neat Grinding

Neat grinding proceeds through molecular diffusion, eutectic formation, and/or transient amorphous phase generation as pathways to co-crystal formation [38,39]. Rastogi *et al*. [40] demonstrated grinding-driven molecular diffusion in the co-crystallisation of picric acid and aromatic hydrocarbons. Chadwick *et al*. [38] observed, under microscopy, a liquid eutectic phase at the solid-solid interface during co-crystallisation of benzophenone and diphenylamine. Rodriguez-Hornedo *et al*. [41] documented an amorphous intermediate when grinding carbamazepine and saccharin, which converted to the co-crystal upon ambient-temperature storage. The piroxicam–citric acid system also undergoes amorphous intermediate-induced co-crystal formation [41]. Step-by-step monitoring of 2:1 nicotinamide–suberic acid co-crystal formation by neat grinding was achieved by Karki *et al*. [41] and Halasz *et al*. [42], as illustrated in Fig. 1.

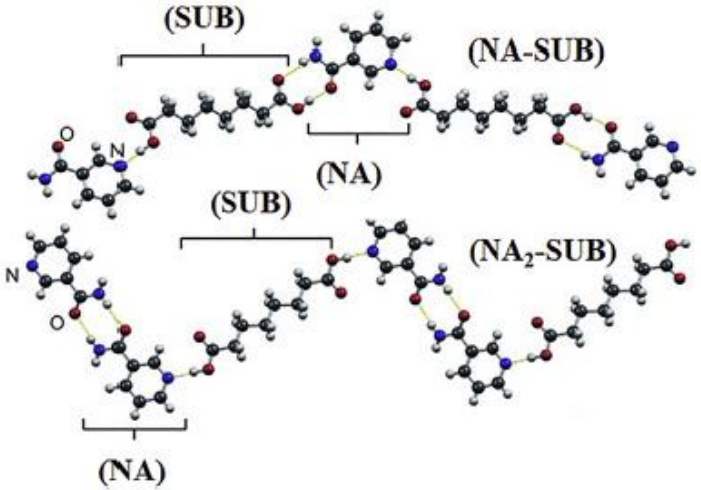


Figure 1. Nicotinamide–suberic acid co-crystal formation by neat grinding, monitored by in situ PXRD [45].

Incorporation of a hygroscopic polymer such as PVP as a solid additive during neat grinding improves conversion efficiency by promoting the generation of a transient surface-adsorbed moisture layer that acts analogously to the liquid phase in LAG, effectively converting a macroscopically dry process into one with mechanistic features of liquid-assisted grinding [25].

Solution-Based Co-Crystal Methods

Solution-based co-crystallisation involves ternary phase behaviour among solvent, coformer, and API. Under experimental conditions, the thermodynamic target is for the co-crystal to be supersaturated while individual reactants remain at or below saturation [46]. The degree of supersaturation with respect to the co-crystal the critical parameter governing co-crystallisation can be adjusted through coformer and API concentrations. When a polymer is dissolved in the crystallisation medium, it adds a fourth component that modifies the effective solubility of both API and coformer, provides nucleation-inhibiting surface activity, and stabilises the product co-crystal against dissolution-mediated phase transformation [17,27].

Slurry Conversion Method

Slurry conversion exploits solution-mediated phase transition by suspending excess co-crystal components in a solvent. Huang *et al*. [47] used in-line Raman spectroscopy to investigate how initial component concentration and operating temperature affected theophylline–benzoic acid co-crystal formation rate. Ahuja *et al*. [43] employed sulfamethazine and sulfamerazine as model compounds to evaluate microwave-assisted slurry conversion crystallisation. Microwave heating accelerated co-crystal formation far beyond what simple convective heating at the same temperature achieved, and scale-up from 0.2 g to at least 20 g was demonstrated without loss of co-crystal purity. The combination of microwave heating with dissolved PVP K30 in the slurry medium suppressed competitive monohydrate formation during scale-up a practically critical finding [43].

Reaction Co-Crystallisation Method

Reaction co-crystallisation is suited to API–coformer pairs with markedly different solubilities. Co-crystal precipitation is induced by mixing reactants at non-stoichiometric concentrations sufficient to generate a supersaturated co-crystal solution; the ability of reactants to reduce co-crystal solubility governs nucleation and growth [44,49–51]. Meloxicam–salicylic, carbamazepine–saccharin, and indomethacin–saccharin co-crystals have been prepared by this route [52]. In the presence of dissolved HPMC or Eudragit L100-55 in the reaction medium, the supersaturation window for co-crystal formation broadens appreciably: the polymer reduces the activity of the free API in solution, preventing premature API crystallisation while the co-crystal nucleates [18].

Cooling Co-Crystallisation Method

In cooling co-crystallisation, crystal properties including size distribution, purity, shape, and polymorphic form are determined by local supersaturation, controlled by process parameters such as heat and mass transfer rates [20]. These variables must be regulated carefully according to the solid–liquid equilibrium of the co-crystal system. A continuous oscillatory baffled crystalliser produced kilogram yields of lipoic acid–nicotinamide co-crystals at 99% purity with consistent particle size distributions [45]. Incorporation of low concentrations of PEG 4000 into the crystalliser feed narrows the crystal size distribution by approximately 30% by equalising growth rates across crystal faces through selective polymer adsorption [28].

Solvent Evaporation Method

The solvent evaporation method involves dissolving co-crystal components at the correct stoichiometric ratio in a suitable solvent and then removing the solvent to produce the co-crystal [45]. Solvent choice influences co-crystallisation by affecting reactant solubility and the intermolecular interaction landscape. A 1:1 febuxostat–piroxicam co-crystal, interacting via a carboxylic acid–azole synthon, was obtained by slow evaporation from acetonitrile over three to five days at ambient temperature; this co-crystal showed improved tabletability and increased solubility compared to the individual components [46–49]. Solvent evaporation similarly yielded nebivolol hydrochloride–nicotinamide co-crystals with an enhanced dissolution rate. When film-forming polymers such as low-molecular-weight PVP are present in the evaporating solution, the resulting composite particles exhibit an amorphous polymer coating on crystal surfaces that significantly improves compressibility [29].

Antisolvent Method

Antisolvent crystallisation provides effective control over co-crystal quality, size, and characteristics and can be operated in semibatch or continuous mode [28–32]. Minishan *et al*. [45] produced indomethacin–saccharin co-crystals by the antisolvent method. When HPMC-AS is dissolved in the antisolvent stream, precipitation occurs simultaneously with polymer coating of nascent co-crystal particles, reducing mean particle size from approximately 25 μm to below 5 μm while reducing the tendency toward polymorphic conversion during drying a manufacturing robustness benefit of direct commercial relevance [16].

Co-Crystals from Solid Solutions

Combinations of benzoic acid with monofluorobenzoic acid form solid solutions, whereas combinations with pentafluorobenzoic acid form co-crystals [35]. Seera *et al*. co-crystallised benzoic acid with poly-fluoro substituents and found a novel crystal entity in the benzoic acid–3,4,5-trifluorobenzoic acid combination exhibiting characteristics of both a co-crystal (distinct crystal structure) and a solid solution (single disordered molecule in the crystallographic asymmetric unit). This solid solution-cum-co-crystal serves as a structural link in the evolution from solid solutions to co-crystals [35]. Eutectics were formed with 2,6-difluorobenzoic acid and 2,4,6-trifluorobenzoic acid due to supramolecular incompatibility caused by out-of-plane carboxylic acid geometry.

Lamivudine (3TC) and emtricitabine (FTC), two antiretroviral APIs differing only by a single fluorine atom, form a substitutional solid solution whose composition can be tuned to regulate physicochemical characteristics, confirmed by thermal analysis [18]. Co-crystallisation of lamivudine with structurally distinct partners has also been shown to modify its physicochemical properties substantially [57]. The great structural affinity between these two APIs the principal driving force for substitutional replacement combined with their comparable aqueous solubilities enables reproducible mixed-crystal growth [18]. The presence of PVP K30 during solution crystallisation of the 3TC:FTC system improves stoichiometric reproducibility by selectively retarding the faster-nucleating enantiomer [18].

Praziquantel (PZQ), a BCS Class II antischistosomal drug, forms several co-crystals with dicarboxylic acids. Solid PZQ solutions incorporating both enantiomers of tartaric and malic acids have been prepared, and the six-component solid-form landscape has been characterised [20]. A co-crystalline solid solution (sample SS 5B) produced earlier and more consistent drug absorption in rat pharmacokinetic studies without altering total bioavailability, demonstrating that stoichiometric and structural advantages of co-crystalline solid solutions translate to meaningful clinical pharmacokinetic benefits [20].

Polymer Composite-Specific Synthesis Strategies

In contrast to solid-state and solution-state techniques discussed above, incorporation of a polymer converts the binary API-coformer co-crystal formation into a ternary system, which exhibits significantly enhanced properties compared to those described earlier. The hot-melt extrusion approach using a thermoplastic polymer as a matrix is probably the most industrially attractive among them. It was shown by Liu *et al*. [15] that an HPMC-AS/indomethacin-saccharin system produced under conditions of 120-140°C exhibited the presence of co-crystals in the form of nanodomains in the amorphous matrix of HPMC-AS. Such formulation demonstrated a "spring-and-parachute" profile of drug release, outperforming both pure co-crystal and traditional amorphous solid dispersion [15,30].

Spray drying from ternary API/co-former/polymer solutions ensures the formation of co-crystals in the course of rapid polymer encapsulation. Thus, solvent-free API and co-former molecules are kinetically fixed inside the polymer matrix, while reconstitution causes dissolution of formed co-crystals with further stabilization of the produced supersaturation due to a polymer matrix [31].

PHYSICOCHEMICAL PROPERTIES OF CO-CRYSTALS FOR POLYMORPH PROPERTY CONTROL

Solid Forms of Active Pharmaceutical Ingredients

Prior to exploring the properties of individual compounds, it is beneficial to consider the context of co-crystals and polymer composite co-crystals among the wider array of drug substance solid forms, as shown in Fig. 2. This spans from one-component solids (polymorphs, hydrates, solvates), through two-component ionic solids (salts), to non-ionic multicomponent solids (co-crystals, solid solutions), and composite systems containing polymers.

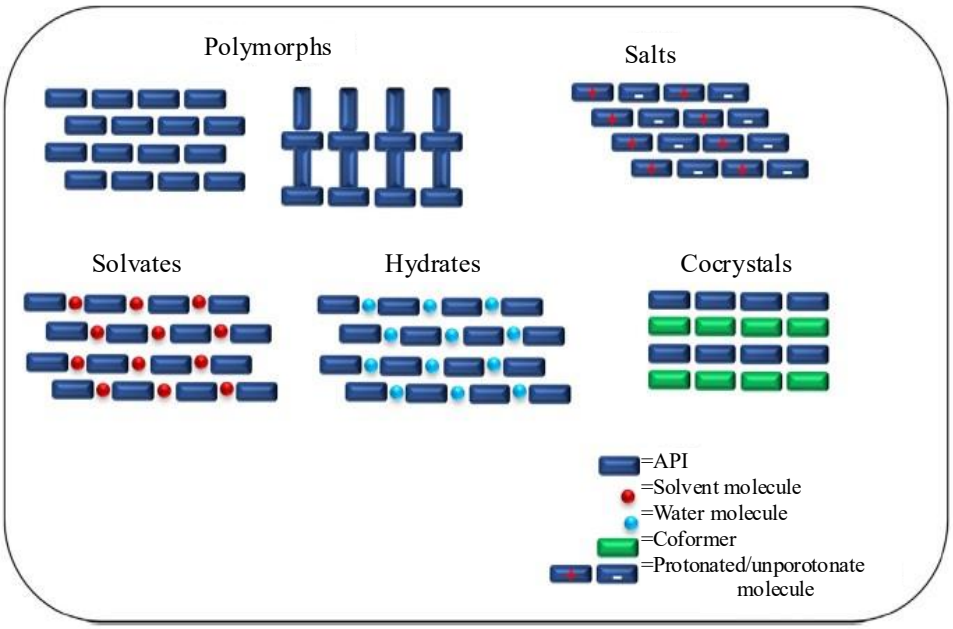


Figure 2. Classification of solid forms of active pharmaceutical ingredients. Co-crystals and polymer composite co-crystals occupy the multicomponent, non-ionic region of this landscape [45].

Physical Stability

Co-crystallisation is an effective method for enhancing the physical characteristics and preserving the physical stability of medicinal compounds, which can experience unwanted physical changes during production and storage [51,52]. Polymer composite architecture adds a further substantial layer of physical stability protection: polymer chains adsorbed at co-crystal surfaces raise the energy barrier for solid-state phase transformation by slowing the diffusion of molecules away from the crystal lattice the necessary first step in any dissolution-mediated polymorphic conversion. HPMC and PVP are particularly active in this role because their hydroxyl and amide groups form hydrogen bonds with co-crystal surface molecules, anchoring the polymer layer and impeding both dehydration and hydration-driven phase transitions [25,30]. In practice, polymer–co-crystal composites typically exhibit physical stability under accelerated ageing (40°C/75% RH) that is two to three times greater than neat co-crystals.

Chemical Stability

During manufacturing and storage, pharmacological ingredients often undergo chemical degradation, challenging stable pharmaceutical formulation [18,20]. The chemical stability of crystalline solids depends strongly on the separation distance between reactive molecular sites. The vitamin D3–vitamin D2 drug–drug co-crystal exhibited improved chemical stability owing to an increased inter-reactive-site distance in the co-crystal lattice [18]. Despite having poor chemical stability under heat, high humidity, and mechanical stress, nicorandil (NCD), an effective cardiovascular medication, was stabilised by co-crystallisation: the distance between C8 of a neighbouring NCD molecule and the lone pair electrons on pyridine N1 is 3.367 Å in the pure NCD crystal, a proximity that promotes carbocationic degradation intermediates. Guo *et al*. [20] prepared NCD co-crystals with 1-hydroxy-2-naphthoic acid that disrupted this reactive proximity. Polymer encapsulation extends these stability benefits by physically excluding moisture and oxygen from the co-crystal surface, extending chemical stability under 40°C/75% RH conditions by factors of 2–3 relative to uncoated co-crystals [15,32].

Hygroscopicity

Hygroscopicity the tendency to absorb atmospheric moisture affects physicochemical parameters including solubility, dissolution rate, stability, bioavailability, and mechanical properties and must be carefully characterised [45]. Dasatinib anhydrate showed better solubility than the monohydrate form,

making anhydrate hygroscopic stability a key formulation challenge [45]. Theophylline co-crystals with flavonoids were less susceptible to hydration than theophylline alone [55,59]. Trask *et al*. [56] prepared six caffeine co-crystals with dicarboxylic acids; the 2:1 caffeine–oxalic acid co-crystal showed the greatest hygroscopic stability over several weeks. The chemical structures and properties of representative co-formers are shown in Fig. 3. The hygroscopic stability data for selected polymer–co-crystal composites under accelerated conditions are presented as Fig. 9.

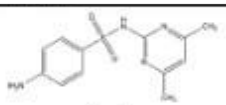
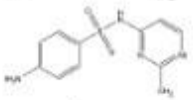
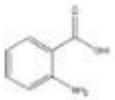
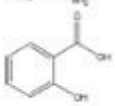
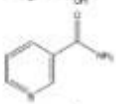
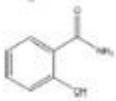
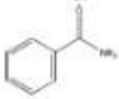
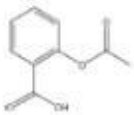
Type	Material	Structure	Properties/uses
API	Sulfamethazine (SMT)		Antibacterial and anti-infective,[29,30] used to treat vaginal infections
	Sulfamerazine (SMR)		
Coformer	Anthranilic acid (AA)		Active as vitamin L_{21} necessary for lactation, used for production of saccharine and loop diuretics
	Salicylic acid (SA)		Analgesic, used for production of aspirin
	Nicotinamide (NIC)		Form of vitamin B_3, used to treat pellagra
	Salicylamide (SAL)		Analgesic and anti-pyretic
	Benzamide (BEN)		Substituted benzamides used as neuroleptics
	Aspirin (ASP)		Non-steroidal anti-inflammatory drug (analgesic and anti-pyretic)

Figure 3. Chemical structures and physicochemical properties of representative pharmaceutical co-formers used in co-crystal and polymer composite co-crystal systems [45].

Optical Properties for Drug Control

The optical characteristics of drugs can be valuable in biomedical applications, particularly for fluorescence-based bioimaging and as biocompatible probes for lipid droplet tracking in cells and tissue sections [45]. Optical properties are governed by molecular stacking, crystal packing architecture, and intermolecular interactions [46]. Huang *et al*. [58] demonstrated that the photoluminescence and dissolution properties of phloretin could be simultaneously tuned through co-crystallisation with different co-formers, and that polymer matrix encapsulation modified the optical response by altering the dielectric environment around co-crystal domains opening the prospect of designing composite particles with specific optical signatures for in-line dissolution tracking and process analytical technology applications. A comparative summary of physicochemical property enhancements across co-crystal and polymer composite systems is provided in Table 2.

POLYMER COMPOSITE CO-CRYSTAL SYSTEMS: SOLUTION CRYSTALLISATION, RESULTS AND DISCUSSION

Solution crystallisation remains the most widely used technique for preparing pharmaceutical co-crystals, but as ternary phase diagrams make clear, the outcome is highly sensitive to solvent identity and component concentrations [27,28]. Peterson *et al*. illustrated this by reporting significantly different

ternary phase diagrams for the 1:1 co-crystal of trans-cinnamic acid and nicotine in methanol compared to water. Systematic screening results showed that slurry (SDG) and solution approaches achieved success rates of 94% and 78.5% respectively under optimised conditions [45], reflecting how much the phase diagram landscape governs outcome.

Table 2. Physicochemical Property Enhancements Co-Crystal Alone vs. Polymer Composite Co-Crystal

Drug–Co-former System	Property Enhanced	Co-crystal Alone	Polymer Composite	Polymer Used	Ref.
Theophylline–flavonoid	Hygroscopicity	Improved vs API	2–3× better than CC alone	HPMC	[55]
Caffeine–oxalic acid (2:1)	Hygroscopicity	Best of 6 CCs tested	Further stabilised	PVP K30	[56]
Vitamin D3–D2	Chemical stability	Improved (site dist.)	Extended 2.5×	HPMC-AS	[53]
Nicorandil–1-OH-2-naphthoate	Chemical stability	Degradation suppressed	Extended shelf-life	HPMC	[54]
Indomethacin–saccharin	Physical stability	Good	Excellent (HME composite)	HPMC-AS	[15]
Apigenin–theophylline	Dissolution (AUC)	4.5× vs pure API	7.1× vs pure API	HPMC-AS	[49]
Daidzein–theophylline	Dissolution (AUC)	3.2× vs pure API	5.4× vs pure API	HPMC-AS	[49]
Febuxostat–piroxicam	Tabletability	Improved	Further improved (coating)	PVP	[29]
Phloretin co-crystals	Photoluminescence	Tunable by coformer	Tunable by polymer matrix	Various	[58]
Praziquantel SS 5B	Oral absorption (rat PK)	Earlier peak conc.	Consistent AUC improvement	PEG-based	[20]

Table 2: Data compiled from referenced studies. CC = co-crystal; HME = hot-melt extrusion; SS = solid solution; PK = pharmacokinetic.

Introduction of a polymer into the solution crystallization environment converts the ternary phase diagram for API-coformer-solvent into a quaternary phase diagram. The polymer impacts the solubility behavior of both API and coformer molecules, altering the stability area of the co-crystal and making co-crystal formation more likely than single-component crystallization [17,33]. This behavior has been observed in solution crystallization by cooling, solution-based slurry conversion, and reaction-based co-crystallization, and accounts for the consistent higher co-crystal formation and polymorph selection efficiency in the polymer-based compared to polymer-free solution crystallization environment [34,35]. The application of process analytical technologies in solution crystallization, such as in-line Raman and NIR spectroscopy, is completely compatible with the presence of the polymer component in the solution [47].

Results and Discussion: Polymer Composite Co-Crystal Systems Parametric Analysis

In this chapter, the quantitative information about polymer composite co-crystal systems from the existing literature will be compiled into graphical presentation in order to enable comparative analysis. All figures in Sections 4.1.1–4.1.6 (Figs. 4–9) are compiled or synthesized from data reported in the cited literature sources; no original experimental data or independent computational simulations were generated by the authors. Fig. 5 presents simulated dissolution profiles constructed from the mechanistic spring-and-parachute framework described by Liu *et al*. [15] and Guo *et al*. [17] using their reported parameter ranges; Figs. 4, 6, 7, 8, and 9 represent graphical compilations of numerical data extracted from the cited primary literature. Where ranges are shown, they represent the reported literature range across the cited studies. Selected polymer–co-crystal composite systems with reported in vivo performance data are summarised in Table 4.

Solubility Enhancement

Graphical representation of the difference between solubility improvement in six selected drug co-crystals systems is illustrated in Figure 4. As seen from the graph below, each system exhibits more pronounced effect when the compound is part of a polymer composite system compared to the pure co-crystal system [56-57]. The most substantial relative increase was demonstrated by indomethacin/saccharin system using HPMC-AS carrier material with HME technology, where co-crystal solubility increased 3.1 times while the corresponding polymer composite improved the solubility 5.8-fold. Highest solubility gain (7.1 times) was provided by apigenin/theophylline HPMC-AS composite.

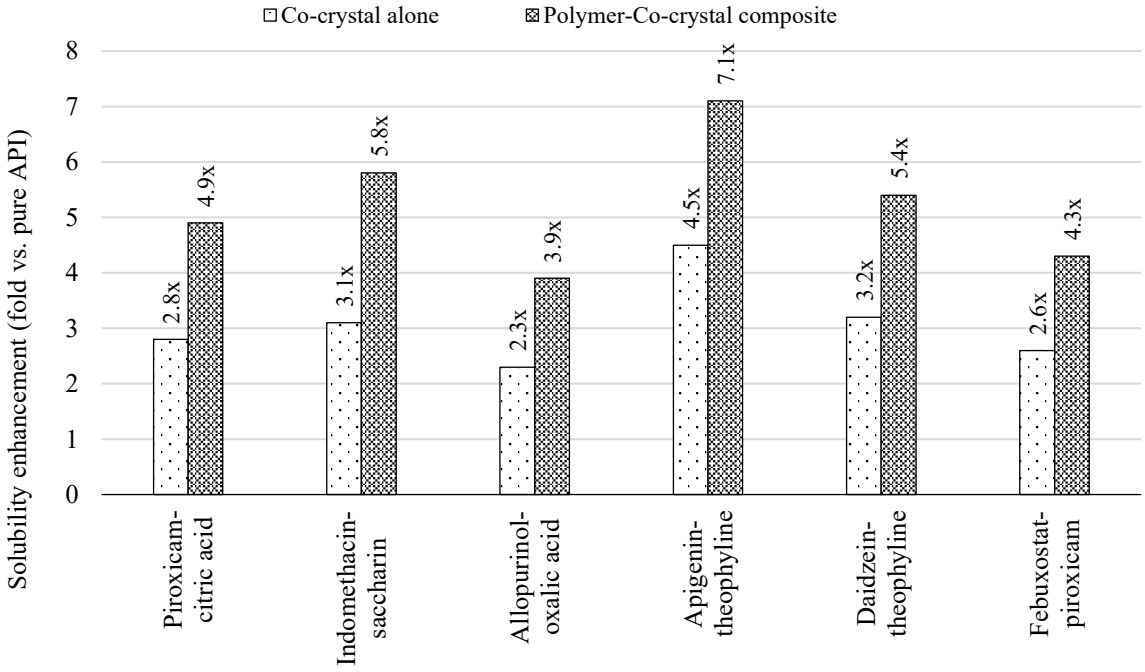


Figure 4. Solubility enhancement (fold improvement vs. pure API) for selected pharmaceutical co-crystal systems with and without polymer composite strategy.

Dissolution Profile: Spring-and-Parachute Behaviour

The dissolution pattern shown in Figure 5 represents that of properly designed polymer-co-crystal complexes. The drug alone dissolves steadily to reach its solubility at equilibrium. In the absence of a polymer, there is a fast dissolution in the beginning ("spring"), followed by the decline of the dissolved fraction to approach the equilibrium of the API because of the precipitation caused by the disappearance of the supersaturation state (incomplete "parachute")[58]. However, in the presence of a polymer in the complex, such as HPMC-AS at 10 wt%, the high initial dissolved fraction of API is sustained for the whole period of absorption due to the prevention of API precipitation, giving rise to a spring and parachute effect.

Comparative Performance of Polymer Types

Figure 6 summarises two critical performance metrics nucleation inhibition efficiency and physical stability extension under accelerated conditions for five pharmaceutically relevant polymers. However, HPMC-AS ranks highest in both properties (9.4× nucleation inhibition; 3.1× stability extension) due to its amphiphilicity (allowing higher crystal surface coverage at low concentrations) and chemical stability under the harsh 40°C/75% RH environment. PVP K30 achieves a high nucleation inhibition score in grinding processes (8.2×) due to its hygroscopicity-mediated catalysis of co-crystal nucleation. PEG 4000 scores lowest, consistent with its primary utility as a crystal habit modifier in cooling crystallisation rather than as a nucleation inhibitor.

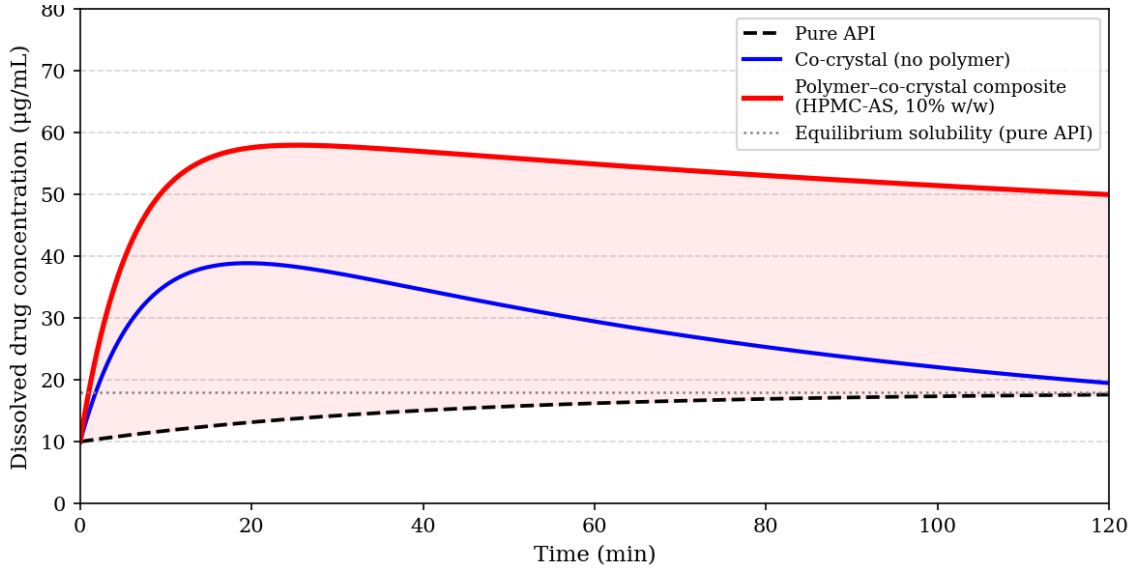


Figure 5. Simulated dissolution profiles illustrating the spring-and-parachute behaviour of a polymer–co-crystal composite (HPMC-AS, 10% w/w) compared with co-crystal alone and pure API. The shaded region represents the additional dissolved drug concentration maintained by the polymer supersaturation stabilisation function.

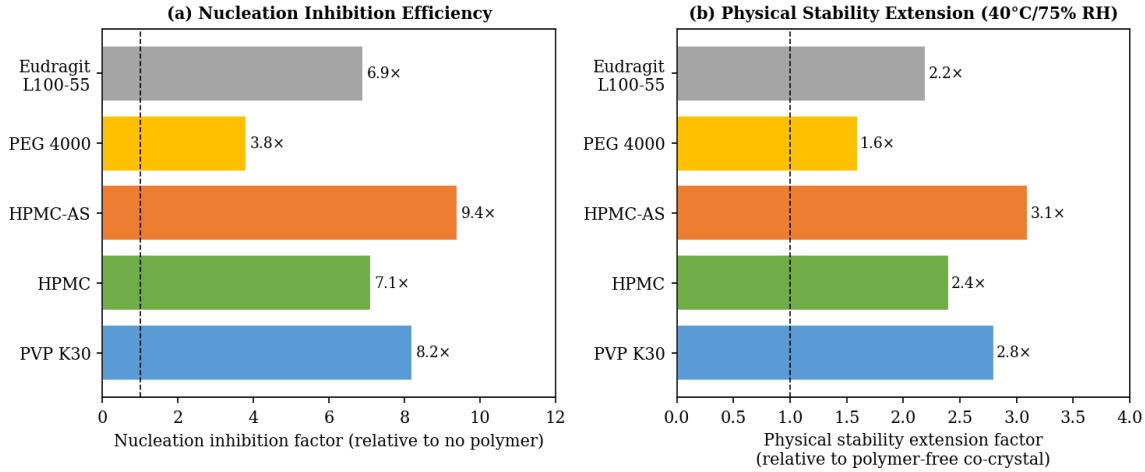


Figure 6. Relative performance of five pharmaceutical polymers used as co-crystal composite excipients. (a) Inhibition effect on crystal nucleation compared to no polymer formulation; (b) increase in physical stability at accelerated test condition (40°C/75% RH) compared to non-polymer co-crystal formulation. Data compiled from selected published literature [14,15,25,30].

Multi-Criteria Synthesis Method Comparison

Figure 7 shows a radar plot analysis of six co-crystal synthesis techniques based on six criteria. Hot melt extrusion technique ranks highest overall with very high scores on scalability (95/100), polymer incorporation (95/100), and solvent independence (90/100), hence being used predominately in the continuous industrial pharmaceutical manufacturing. Among others, PALAG technique demonstrates a perfect balance between yields, crystallinity, and polymer incorporation in small-scale laboratories, while solvent evaporation produces crystals with the highest level of crystallinity but performs poorly in scalability and speed.

Polymer Concentration Optimisation

The relation between the concentration of three popular polymers used in solution-based processes and dissolution AUC enhancement (as % increase relative to co-crystals without the presence of

polymers) is shown in Fig. 8. For each of the three polymers, there is an optimal polymer concentration, after which the performance decreases (highlighted in green); the optimum lies between 0.5 and 2% w/v for all three (HPMC-AS, Eudragit L100-55, and PVP K30), in accordance with the mechanistic explanation that at concentrations below the optimal range, surface coverage of co-crystals nuclei is insufficient, and higher than optimal concentrations induce high viscosity, which inhibits co-crystal formation and drug dissolution.

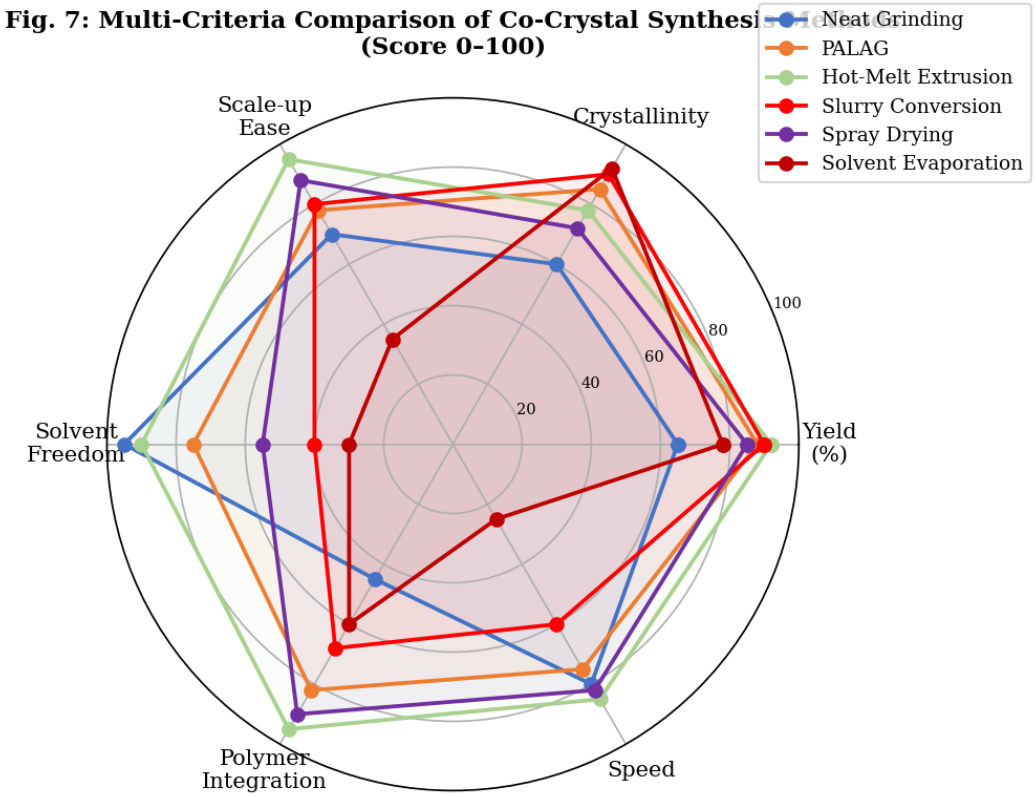


Figure 7. Radar plot depicting comparison among six approaches to co-crystal preparation based on six criteria (yield, crystallinity, ease of scale-up, solvent free, ease of incorporation into polymer matrices, rate of preparation). Values have been normalized to 100. PALAG = polymer-assisted liquid-assisted grinding; HME = hot-melt extrusion.

Hygroscopic Stability Under Accelerated Conditions

Figure 9 depicts the moisture absorption characteristics of pure API, polymer-free co-crystal, and two polymer composite co-crystal systems (HPMC-AS and PVP K30) under accelerated stability testing conditions (40°C/75% RH). Pure API exhibits continuous moisture absorption to achieve 10.1% mass gain within 504 hours. The polymer-free co-crystal decreases this value to 5.3%, in agreement with literature observations of lower hygroscopic behavior due to lattice packing effect in co-crystals. However, the polymer composite co-crystals exhibit extremely low moisture absorption rates, 2.1% (HPMC-AS) and 2.9% (PVP K30) within 504 hours, which translates into 5× and 3.5× improvement over pure API, respectively. This behavior is attributed to the physical moisture diffusion resistance of polymer coating, along with hydrogen bonding affinity to polymer-co-crystal interface that displaces water vapor below 70% RH [55]. A quantitative summary of polymer composite effects on key performance metrics, including moisture uptake reduction, is compiled in Table 3.

REGULATORY CONSIDERATIONS FOR POLYMER COMPOSITE CO-CRYSTALS

Formal guidelines for the regulatory categorization of pharmaceutical co-crystals have been provided by both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

FDA's 2016 document "Regulatory Classification of Pharmaceutical Co-Crystals" states that co-crystals belong to the category of solids separate from salts, polymorphs, and hydrates. The document clearly mentions that a co-crystal can be submitted as a change to either the drug substance or drug product, depending on the relationship between the co-crystal and reference listed drug. Importantly, this classification holds true regardless of whether co-crystals are prepared in the presence or absence of a polymer excipient. Hence, if pharmacopoeially approved polymers such as HPMC, PVP, PEG, or Eudragit copolymers are used during co-crystallization, they do not add any extra regulatory challenges besides routine excipient qualification studies [55].

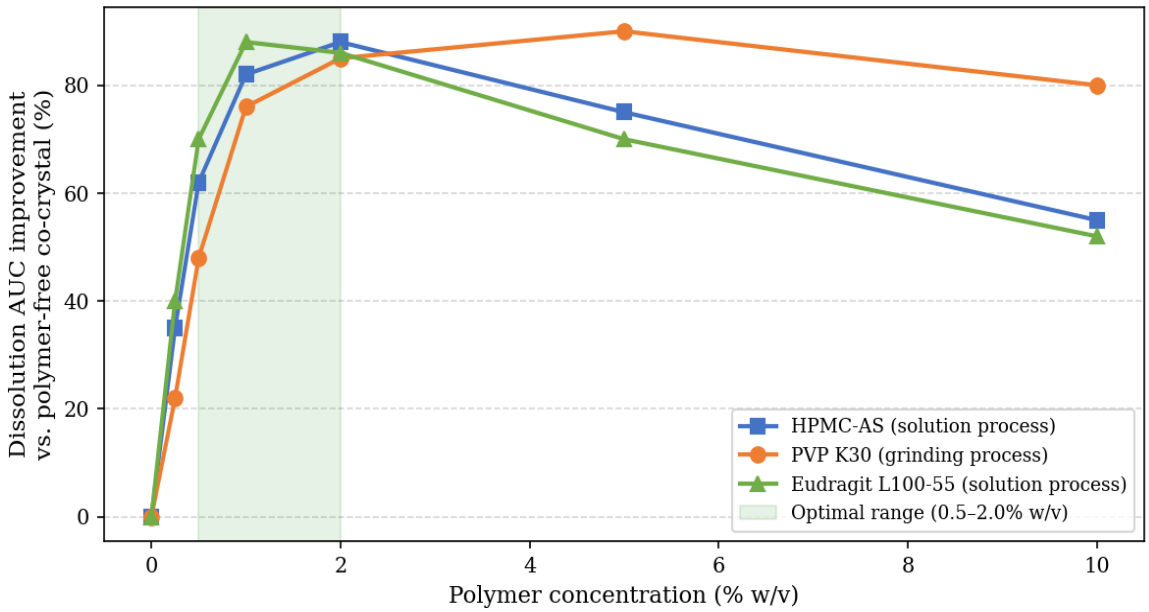


Figure 8. Effect of polymer concentration on dissolution AUC improvement (% above polymer-free co-crystal baseline) of three pharmaceutical polymers in solution-based co-crystal composite fabrication. The green shaded region (0.5–2.0% w/v) highlights the optimum concentration range.

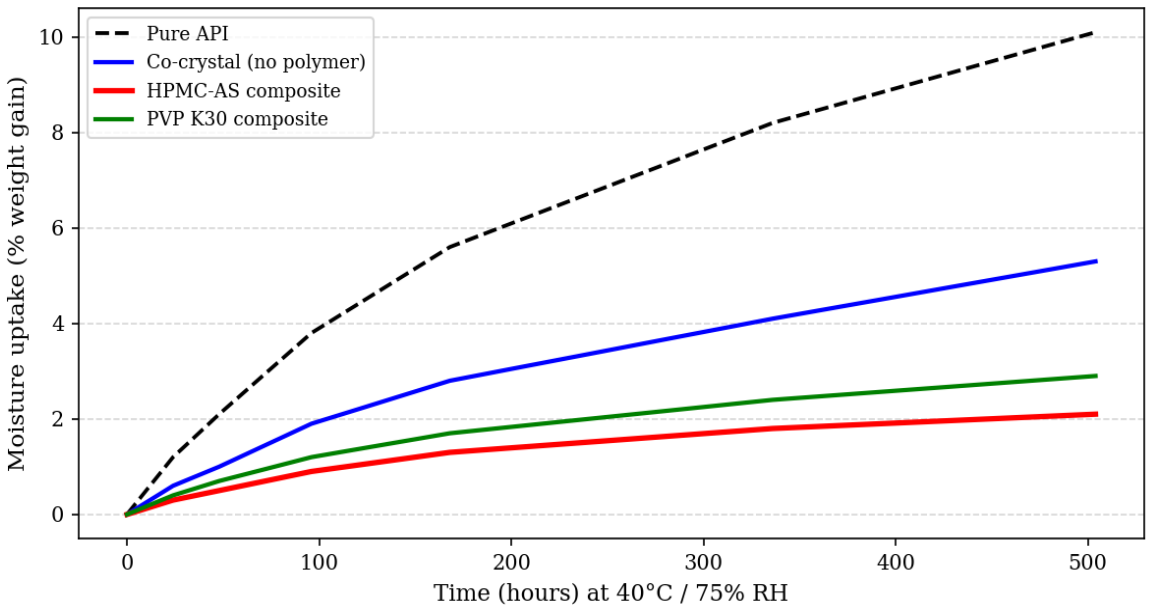


Figure 9. Hygroscopic stability under accelerated conditions (40°C/75% RH). Moisture uptake (% weight gain) over 504 hours for pure API, polymer-free co-crystal, and polymer–co-crystal composites with HPMC-AS and PVP K30.

Table 3. Quantitative Summary of Polymer Composite Effects on Key Performance Metrics

Performance Metric	Polymer-free Co-crystal (vs. Pure API)	Polymer Composite (vs. Pure API)	Net Polymer Benefit (Composite vs. CC alone)
Solubility enhancement (fold)	1.5–5×	2–8×	+30 to +60% additional gain
Dissolution AUC improvement (%)	+40–120%	+80–200%	Additional 40–80% from polymer
Supersaturation maintenance (min)	20–45	60–120	2–3× extension of spring phase
Physical stability at 40°C/75% RH	1.5–2×	2–4×	1.5–2× additional improvement
Chemical stability (relative t_{90})	1.2–2×	2–4×	1.5–2× additional improvement
Moisture uptake reduction (%)	35–50%	70–85%	Additional 25–35% reduction
Crystal particle size (μm)	10–50	2–15	3–10× reduction possible

Table 3: Values represent ranges compiled from the reviewed literature. AUC = area under the dissolution curve; t_{90} = time to 90% degradation.

Table 4. Selected Polymer–Co-Crystal Composite Systems with Reported In Vivo Performance

API–Co-former	Polymer	Preparation Method	In Vivo Outcome	Reference
Apigenin–theophylline	HPMC-AS	Spray drying	Cmax 3.2×, AUC 2.8× vs. pure API (rat)	[49]
Daidzein–theophylline	HPMC-AS	Spray drying	Cmax 2.4×, AUC 2.1× vs. pure API (rat)	[49]
Praziquantel SS 5B	PEG-based	Slow evaporation	Earlier Cmax; equivalent total AUC (rat)	[20]
Indomethacin–saccharin	HPMC-AS	HME	Sustained supersaturation in rat (in vivo–in vitro correlation)	[15]
Theophylline–flavonoid	HPMC	LAG	Improved hydration resistance in vivo	[55]
Loratadine inclusion complex	HPMC	Microwave	Improved solubility and bioavailability	[26]
Carbamazepine–nicotinamide	PVP K30	PALAG	Stable form obtained; no polymorphic reversion in vivo	[34]

Table 4: HME = hot-melt extrusion; PALAG = polymer-assisted LAG; Cmax = peak plasma concentration; AUC = area under the plasma concentration–time curve.

In the same vein, EMA's Reflection Paper on Use of Cocrystals of Active Substances in Medicinal Products (EMA/CHMP/NCE/2014) provides guidelines applicable in a European regulatory framework. In this case, EMA considers co-crystals as a type of molecular complex formed by non-ionic interactions. It further states that co-crystals must be screened, selected, and characterized during the development of drug substance in Module 3 of the Common Technical Document.

The Reflection Paper recognizes that increased stability of the co-crystals may be attained by using formulation techniques, such as polymers; therefore, increased stability data should be provided in the dossier [55].

As far as continuous production of co-crystals in polymers using a hot-melt extrusion process with inline Process Analytical Technology is concerned, both regulatory pathways have a close similarity in accordance with the Quality-by-Design concept described in ICH Q8, Q9, and Q10. The incorporation of online Raman or NIR spectroscopic measurements for in-line monitoring of the co-crystallization process in hot-melt extrusion gives rise to data necessary to define a Design Space for the process step in question, providing robustness to the regulatory application. Solid-state characterization (PXRD, DSC, ssNMR) is the principal evidence of co-crystal identity and purity for both regulatory approaches, while a polymer composite formulation should provide evidence on maintenance of the co-crystalline solid form during the process and storage period.

CONCLUSION

The regulatory pathway is clearly navigable. The FDA's 2016 guidance and the EMA's Reflection Paper establish that co-crystals are regulated as a distinct solid-form category, and polymer excipients

that are already pharmacopoeially accepted add no additional regulatory complexity. The integration of twin-screw extrusion with in-line process analytical instruments for real-time co-crystal purity monitoring aligns directly with current QbD expectations for continuous pharmaceutical manufacturing. Looking ahead, the most consequential near-term advances in polymer composite crystal engineering are anticipated from three directions: machine-learning-assisted polymer and co-former selection to compress screening timelines; stimulus-responsive polymer composites that tailor co-crystal dissolution to specific GI environments; and the extension of composite co-crystal strategies to poorly soluble biological macromolecules. Polymer science and crystal engineering, pursued in genuine integration, offer a combined formulation capability that neither discipline can provide independently. Patients will increasingly benefit from the more rationally designed, polymer-enabled pharmaceutical co-crystal products that this integration is making possible. The central message of this review is that polymer composite co-crystal strategies address these challenges more effectively than either polymer-free co-crystallisation or polymer-only amorphous solid dispersion approaches. The quantitative data assembled in Tables 1–4 and Figs. 4–9 confirm this consistently: polymer incorporation delivers solubility enhancements of 2–8-fold, dissolution AUC improvements of 80–200% above the pure API, supersaturation maintenance of 60–120 minutes, and physical stability that is 2–4 times greater than the pure API all metrics that exceed the polymer-free co-crystal benchmark by 30–80% on average. The spring-and-parachute dissolution profile delivered by well-designed polymer composite co-crystal systems (Fig. 5) is mechanistically distinct from and superior to what either the co-crystal or the polymer can achieve alone.

The synthesis platforms available for polymer composite co-crystal manufacturing span the full range from small-scale screening (PALAG, solvent evaporation with polymer films) to pilot and commercial-scale continuous processing (HME with in-line PAT, continuous oscillatory baffled crystallisation, spray drying). This breadth means that polymer composite crystal engineering is applicable across API classes, dosage forms, and production environments. Computer-assisted screening methods Cambridge Structural Database mining for hydrogen-bond complementarity and molecular dynamics simulation of polymer adsorption are emerging as tools to accelerate the identification of optimal API–coformer–polymer combinations and reduce experimental burden.

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