



Comprehensive Review on Solubility Enhancement Using Co-Crystallization

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ABSTRACT:

The poor aqueous solubility of a vast number of new drug candidates represents one of the most persistent challenges in pharmaceutical development, often severely limiting their oral bioavailability and therapeutic efficacy. While numerous strategies exist to mitigate this issue, solid-form manipulation, and specifically pharmaceutical co-crystallization, has emerged as a particularly powerful, versatile, and rational approach. This review provides a comprehensive synthesis of the co-crystallization field, tracing its evolution from a foundational concept to a mature, commercially viable technology. It begins by examining the seminal papers that established co-crystals as a new paradigm in drug design, supported by the fundamental principles of crystal engineering and supramolecular chemistry. The review then addresses the practical challenges that arose during early development, such as high-throughput screening, physical stability, scalable manufacturing, and initial regulatory uncertainty. Subsequently, it explores the modern landscape in detail, highlighting the pivotal shift from empirical screening towards rational, predictive design using computational tools like machine learning and crystal structure prediction, the development of robust and continuous manufacturing processes, and the establishment of clear regulatory pathways guided by Quality by Design (QbD) principles. Finally, it showcases cutting-edge applications through case studies that demonstrate not only enhanced in vitro solubility but also proven in vivo performance across critical therapeutic areas, and discusses advanced concepts like the salt-co-crystal continuum, pointing towards a future of increasingly efficient, predictable, and sophisticated solid-form development.

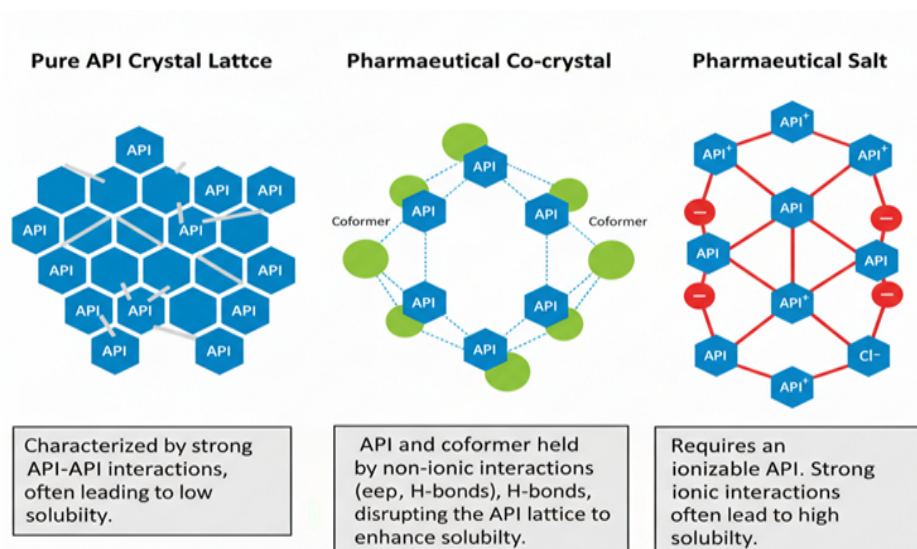
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Salt- Crystal continuum

INTRODUCTION

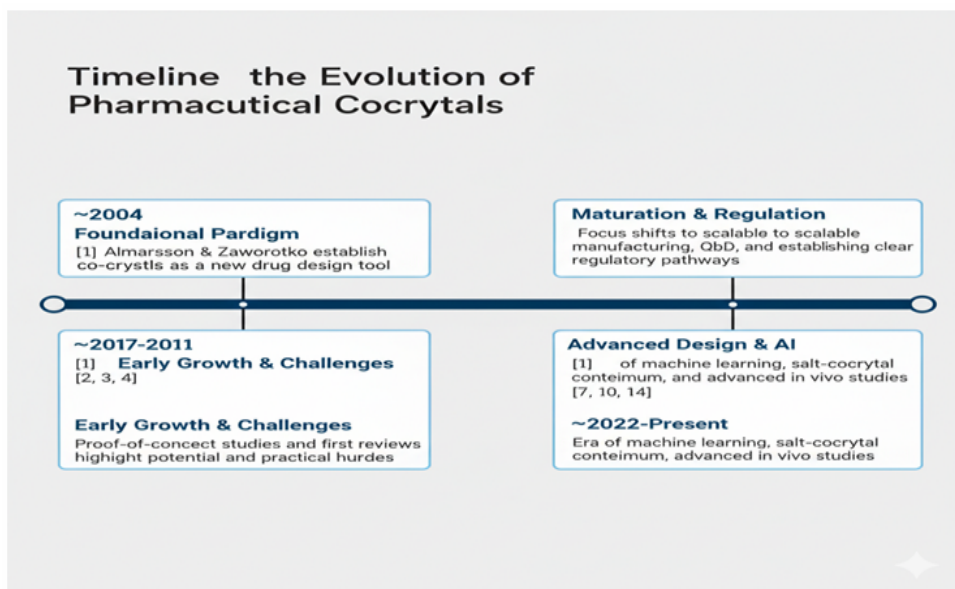
A significant and growing portion of new chemical entities (NCEs) emerging from modern drug discovery pipelines suffer from poor aqueous solubility, classifying them as Biopharmaceutics Classification System (BCS) Class II (low solubility, high permeability) or IV (low solubility, low permeability) compounds. This physicochemical property severely restricts their dissolution rate, which is often the rate-limiting step for oral absorption, thereby hindering their bioavailability and clinical potential [9]. While numerous strategies exist to enhance solubility—including salt formation, particle size reduction (nanonization), lipid-based formulations, and amorphous solid dispersions—each has its own limitations. Salt formation, for instance, is restricted to APIs containing ionizable functional groups, while amorphous forms, despite their high apparent solubility, often suffer from physical instability and a tendency to recrystallize. In this context, the engineering of a drug's solid form has become a critical and strategic area of research. Pharmaceutical co-crystallization has established itself as a premier strategy within this domain. A co-crystal is formally defined as a single crystalline phase composed of an Active Pharmaceutical Ingredient (API) and one or more intrinsically benign cofomers in a defined stoichiometric ratio, held together by non-ionic interactions such as hydrogen bonds, π - π stacking, and van der Waals forces [1]. Unlike salts, co-crystallization is not limited to ionizable APIs, thus vastly expanding its applicability across the chemical space. The fundamental premise is that by altering the crystal lattice—its packing energy and hydrogen-bonding network—one can modify key physicochemical properties—most notably solubility, dissolution rate, and even mechanical properties like compressibility—without altering the molecular structure of the API itself [1, 4].



This review provides a synthesized and in-depth analysis of the field's progression, leveraging key foundational papers, comprehensive reviews, and cutting-edge research to chart the development of co-crystallization from a concept to a practical and indispensable solution for solubility enhancement.

II. THE FOUNDATIONAL PARADIGM: ESTABLISHING CO-CRYSTALLIZATION AS A VIABLE STRATEGY

The modern era of pharmaceutical cocrystals was catalyzed by a landmark publication by Almarsson and Zaworotko that framed them as a "new paradigm in the science of crystal engineering and drug design" [1]. This influential work did more than just introduce a technique; it articulated the immense potential of co-crystals to systematically address longstanding pharmaceutical challenges, positioning them as a distinct and rational alternative to traditional solid forms like salts, polymorphs, and solvates. It shifted the focus from serendipitous discovery to a more predictable, design-oriented approach, suggesting that solid-state properties could be engineered with the same precision as molecular structure.



The theoretical bedrock for this rational design is the concept of supramolecular synthons, as championed by Desiraju [5]. Synthons are recurring, predictable patterns of intermolecular interactions that guide the assembly of molecules into a crystal lattice. By understanding these hydrogen-bonding motifs—such as the robust carboxylic acid dimer or the pyridine-carboxylic acid heterosynthon—scientists could begin to rationally select cofomers likely to form stable co-crystals with a given API [5]. This principle was quickly translated into practice, with early experimental work by Aakerøy et al. demonstrating that co-crystals could be successfully engineered to improve the dissolution profiles of poorly soluble drugs like fluoxetine hydrochloride, providing a crucial proof-of-concept that linked crystal engineering theory directly to pharmaceutical benefit [4].

Following this initial surge of interest, the first major reviews began to consolidate the burgeoning knowledge. The work by Schultheiss and Newman systematically cataloged known pharmaceutical co-crystals, analyzed their properties, and emphasized the critical role of solid-state characterization techniques like Powder X-ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), and Single-Crystal X-ray Diffraction (SCXRD) in confirming their formation and understanding their structure [2]. These early publications laid the essential groundwork, establishing the core principles, vocabulary, and

experimental protocols that would define the field for the next decade. However, as the field grew, it became clear that translating this academic promise into a commercially viable product would require overcoming significant practical hurdles.

III. THE PATH TO PRACTICE: CHALLENGES AND MATURATION OF THE FIELD

While the initial promise was immense, the path from the laboratory bench to a commercial product was fraught with challenges. A critical review by Daurio et al. served as a reality check, highlighting the key hurdles that needed to be overcome for co-crystals to become a mainstream pharmaceutical technology [3]. These challenges were multifaceted and required a concerted effort from the scientific community to address:

Screening and Selection: The difficulty in efficiently and reliably finding a suitable cofomer from a vast pool of Generally Recognized As Safe (GRAS) molecules. Early methods were often labor-intensive and based on trial-and-error. Techniques like neat grinding (mechanochemistry) and liquid-assisted grinding (LAG), where a small amount of solvent is added to facilitate molecular mobility, became standard for initial screening. However, scaling these to high-throughput platforms that could test hundreds of cofomers quickly was a significant logistical and analytical challenge.



Physical and Chemical Stability: Ensuring the co-crystal remains stable throughout its entire lifecycle is paramount. This includes:

Solid-State Stability: Resistance to phase transformations induced by environmental stressors like humidity and temperature. A co-crystal stable at room temperature might dissociate or convert to a different polymorph under humid conditions.

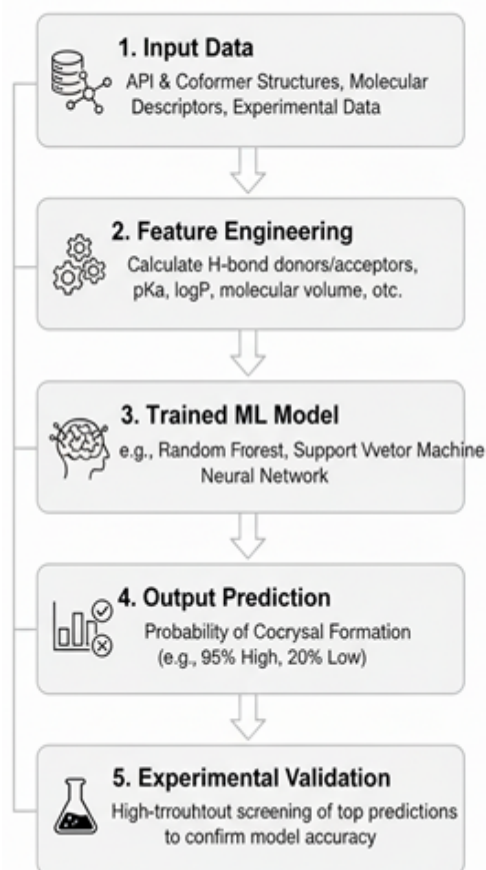
Solution-State Stability: The co-crystal must be stable long enough in the dissolution medium to deliver the "spring and parachute" effect. If it dissociates too rapidly, the API may precipitate out as its less soluble form, negating any benefit

Mechanical Stability: The co-crystal must withstand the stresses of manufacturing processes like milling and tableting without converting back to the pure API.

A critical aspect of this stability challenge is cocrystal polymorphism, where a single API-coformer pair can crystallize in multiple distinct packing arrangements. A data-driven analysis of the Cambridge Structural Database (CSD) confirmed that while less common than in single-component APIs, cocrystal polymorphism is a real and significant phenomenon (occurring in ~6% of systems), representing a quantified risk that must be managed during development, as different polymorphs can have vastly different solubilities and bioavailabilities [20].

Scalable Manufacturing: Developing robust, cost-effective, and scalable manufacturing processes that could produce co-crystals with consistent quality, moving beyond batch-wise grinding to industrially relevant techniques. Early lab-scale methods were often difficult to control and scale, posing a major barrier to commercialization.

Machine Learning Workflow for Co-crystal Prediction



Regulatory Uncertainty: In the early 2010s, there was significant ambiguity from regulatory bodies like the FDA and EMA regarding how co-crystals would be classified. Were they a new molecular entity requiring full clinical trials, or a new solid form of an existing API? This uncertainty created a major investment risk. The release of the FDA's draft guidance on cocrystals in 2013, followed by the final guidance in 2016, was a pivotal moment that provided much-needed clarity and de-risked the development process [3, 8].

This period of self-reflection was crucial, as it directed the research community's efforts toward solving these practical problems and transforming the technology from an academic curiosity into a viable industrial platform.



IV. THE MODERN LANDSCAPE: DESIGN, MANUFACTURING, AND REGULATION

In response to the identified challenges, the field has matured significantly over the last decade, with major advances in design, manufacturing, and regulatory science.

4.1. From Trial-and-Error to Rational, Predictive Design

The most significant evolution has been the shift from empirical screening to rational, predictive design, directly addressing the screening bottleneck. Modern reviews now emphasize a multi-pronged computational approach [7].

Data-Driven Methods (Machine Learning): ML models are trained on vast datasets of known cocrystals and non-cocrystals. By analyzing molecular descriptors, hydrogen-bonding patterns, and coformer properties, these models can predict the probability of cocrystal formation with high accuracy, allowing researchers to prioritize the most promising cofomers for experimental validation [10].

Physics-Based Methods (Crystal Structure Prediction - CSP): As the ultimate form of rational design, CSP uses computational chemistry to predict all possible crystal packing arrangements (polymorphs) for a given API-coformer pair. This not only predicts if a cocrystal will form but also provides its likely crystal structure, energy, and properties, allowing for a thorough risk assessment of potential polymorphism before any experiment is done [19].

Hybrid Methods (Hydrogen Bond Propensity): Sitting between ML and CSP, tools like COSMO-RS or hydrogen bond propensity (HBP) calculations can rapidly estimate the likelihood of specific hydrogen-bonding interactions, providing a quick and chemically intuitive filter for coformer selection.

4.2. Scalable Manufacturing and Process Innovation

To address the scale-up challenge, researchers have successfully developed and optimized several industrially relevant, continuous manufacturing processes, moving beyond lab-scale batch methods [6].

Hot-Melt Extrusion (HME): This solvent-free, continuous process involves melting a physical mixture of API and coformer and forcing it through a die. The high shear and temperature promote cocrystal formation in a single step. It is highly efficient and can be monitored in real-time using Process Analytical Technology (PAT) tools like Raman spectroscopy to ensure quality [12].

Spray Drying: As a powerful alternative, spray drying is particularly advantageous for APIs that are thermally sensitive and would degrade in HME. It involves atomizing a solution of the API and coformer into a hot chamber, where the solvent rapidly evaporates, inducing cocrystal formation. This continuous process also produces spherical particles with excellent flowability, which is ideal for direct compression into tablets [18].

Twin-Screw Wet Granulation: Another continuous process where a liquid binder (often containing the coformer in solution) is added to API powder in a twin-screw extruder, promoting cocrystal formation during granulation. This integrates cocrystal formation directly into a standard pharmaceutical unit operation.

The adoption of these continuous methods aligns with the industry's push towards "Green Chemistry" by reducing solvent waste and improving overall process efficiency and quality control.

4.3. Navigating the Regulatory Pathway

The initial regulatory ambiguity has been largely resolved, replaced by a clear framework built on Quality by Design (QbD) principles [8]. The FDA's guidance classifies cocrystals as a distinct API solid form. The key requirements now include:

Justification of Coformer: A thorough safety assessment of the coformer, often leveraging its GRAS status or existing use in approved drugs.

Thorough Characterization: A complete solid-state characterization package, including a deliberate search for cocrystal polymorphs, is mandatory.

Establishment of a Design Space: For manufacturing, developers are encouraged to define a multidimensional "design space" of critical process parameters (e.g., temperature, solvent composition, stoichiometry) within which the cocrystal can be consistently produced.



Robust Control Strategy: A comprehensive control strategy must be implemented to ensure the final product consistently meets its critical quality attributes (CQAs), such as purity, correct polymorphic form, and dissolution profile.

This clarity has de-risked the development process and provided a clear roadmap for companies seeking to bring co-crystal products to market.

V. CURRENT APPLICATIONS AND ADVANCED CONCEPTS

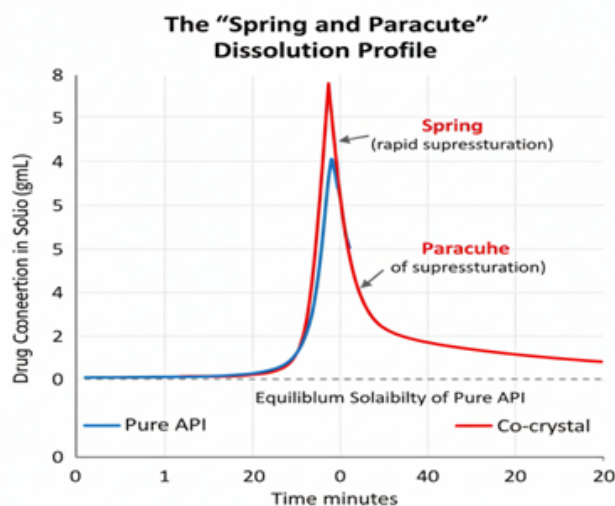
The maturity of the field is best demonstrated by its current applications and the emergence of more advanced concepts.

5.1. Proven Success: Case Studies in Solubility and Bioavailability

Numerous recent studies showcase the successful application of co-crystallization across a wide range of therapeutic areas, proving its value beyond academic interest. A typical example involves the formation of a Telmisartan-Theobromine co-crystal, which exhibited a significantly enhanced dissolution rate for this major BCS Class II API [9]. The technology's impact is also seen in critical global health areas. For instance, a cocrystal of the antiretroviral drug Abacavir—a WHO Essential Medicine—with malonic acid showed a ~4-fold increase in solubility and, most importantly, a ~2.5-fold increase in in vivo bioavailability, demonstrating its potential to improve life-saving HIV treatments and reduce patient dosing burden [17]. This complements other successful preclinical studies, such as work on NSAIDs that confirmed enhanced pharmacokinetic profiles in animal models [15]. Moving beyond the lab, the ultimate proof of concept is a product that has reached the market, with case studies detailing the development and regulatory approval of the Eszopiclone-Malic Acid co-crystal providing a real-world blueprint for the entire process [11].

5.2. Deepening Mechanistic Understanding

The field is also moving beyond simply measuring dissolution to understanding its underlying mechanisms with quantitative rigor.



Thermodynamic Modeling: The "spring and parachute" effect can now be quantitatively understood through thermodynamic modeling. A proposed thermodynamic cycle relates the cocrystal's solubility advantage directly to the difference in lattice energies between the cocrystal and the pure API, as well as the solubility of the cofomer. This provides a powerful predictive tool for formulation scientists to estimate the potential solubility gain before committing to synthesis [16].

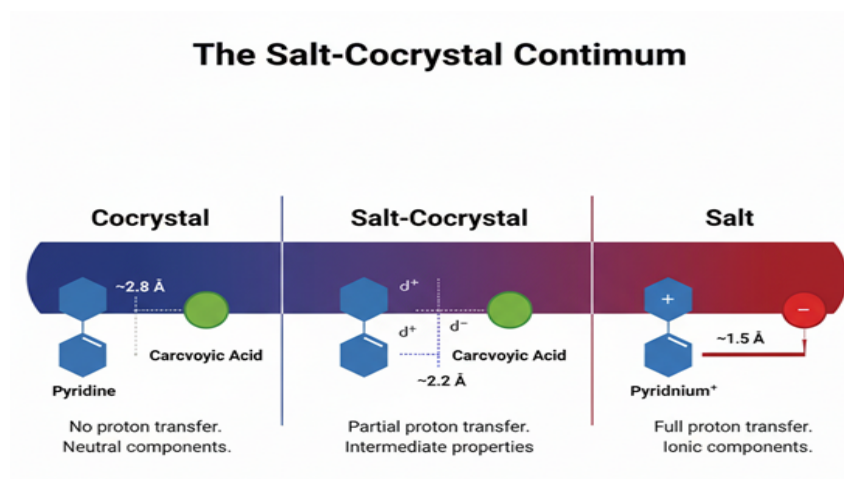
Real-Time Dissolution Analysis: Using advanced analytical techniques like in situ Raman spectroscopy or synchrotron X-ray diffraction, researchers can now observe the dissolution of a cocrystal in real-time. This provides critical insights into the "spring and parachute" phenomenon, revealing how the cofomer can inhibit the nucleation and growth of the stable, less soluble API form, thereby maintaining supersaturation [13].

5.3. Expanding the Toolkit: Advanced Solid Forms

Innovation continues at the conceptual level, pushing the boundaries of what is possible with multicomponent crystals.

The Salt-Cocrystal Continuum: For APIs that are too weak to form stable salts, these intermediate solids, where proton transfer is partial, can offer a unique balance of high solubility and stability. Gao et al. demonstrated this strategy for weakly basic drugs, showing it can modulate

properties in ways that simple salts or cocrystals cannot, thus expanding the applicability of solid-form engineering to more challenging molecules [14].



Ternary and Higher-Order Cocrystals: The field is moving beyond simple 1:1 binary cocrystals to explore more complex systems. Ternary cocrystals, consisting of an API and two different cofomers, can be designed to synergistically combine benefits, such as one cofomer enhancing solubility while another improves stability or processability.

5.4. The Frontier of Discovery: AI-Assisted Screening and Digital Twins

The frontier of co-crystal discovery is being driven by data science and the concept of a fully integrated digital workflow. The development of ML models by Kumar et al. represents a paradigm shift in screening [10]. These models, trained on thousands of data points, can predict co-crystal formation with high accuracy, drastically reducing the need for resource-intensive experimental screening. The ultimate vision is the creation of "digital twins" for cocrystal development, where a computational model of the entire process—from molecular interaction and thermodynamic prediction to manufacturing simulation—is created to optimize development and de-risk the project before any physical experiments are run. This heralds a new era of AI-assisted drug development where the discovery of optimal solid forms becomes faster, cheaper, and more predictable.

VI. CONCLUSION AND FUTURE PERSPECTIVES

The journey of pharmaceutical co-crystallization, from a visionary concept proposed in the early 2000s [1] to a mature, regulated, and commercially successful technology today, is a testament to the power of interdisciplinary research, blending crystal engineering, pharmaceutical sciences, and data analytics. The field has successfully navigated its initial challenges by embracing rational design [7, 19], developing scalable and continuous manufacturing processes [6, 12, 18], and establishing a clear regulatory framework guided by QbD principles [8]. The evidence is no longer limited to in vitro studies; it is now supported by real-world case studies of approved products [11] and compelling in vivo data across critical therapeutic areas like antivirals and anti-inflammatories that confirms therapeutic benefit [15, 17].

Looking forward, the trajectory of the field is expanding beyond its primary focus on solubility, with new and exciting applications emerging that will further solidify its role in modern drug development:

Engineering for Manufacturability: The future will see cocrystals increasingly used to solve manufacturing challenges. Research is now demonstrating that co-crystallization can be a powerful tool to intentionally engineer the mechanical properties of an API, such as its plasticity and tabletability. By forming a cocrystal with a cofomer that imparts desirable compaction characteristics, formulators can overcome issues of poor powder flow or capping in tablets, leading to



more robust and efficient manufacturing processes [21].

Expanding to Non-Oral Drug Delivery: The application of cocrystals is breaking free from the confines of oral dosage forms. Innovative research is exploring their use for transdermal delivery, where a "cocrystal prodrug" can enhance the flux of a lipophilic drug through the skin by increasing its solubility in skin fluid [22]. This opens up new possibilities for non-invasive delivery of drugs that previously required injections, improving patient comfort and compliance.

Designing for Patient-Centric Formulations: Cocrystallization is poised to play a key role in creating formulations for special populations. A particularly promising area is taste masking for bitter APIs, which is critical for pediatric and geriatric patients who cannot swallow large pills. By forming a cocrystal that reduces the API's solubility in saliva, its interaction with taste receptors is minimized, enabling the creation of more palatable liquid or orally disintegrating tablet formulations [23].

Enhancing Chemical and Physical Stability: Beyond solubility, cocrystals are being recognized as a strategy to improve the intrinsic stability of a drug. For APIs that are sensitive to degradation by light, heat, or humidity, cocrystallization can offer a protective effect. The new crystal packing can physically shield photosensitive functional groups or alter the micro-environment to prevent hydrolysis, thereby extending the drug's shelf-life and reducing the need for specialized packaging [24].

Enabling Next-Generation Combination Therapies: The frontier of cocrystal research lies in the creation of multi-component systems containing two or more different APIs. The successful synthesis of cocrystals that combine two antihypertensive drugs into a single crystalline entity points to a future where entire fixed-dose combination therapies can be engineered from the bottom up. This could revolutionize combination products by ensuring a fixed API ratio, simplifying manufacturing, and improving patient adherence [25].

In conclusion, the integration of artificial intelligence and machine learning will continue to accelerate and de-risk the discovery phase [10]. Simultaneously, the exploration of these new

application spaces—mechanical enhancement, non-oral delivery, patient-centric design, stability improvement, and combination therapy—will expand the technology's reach and impact. As our mechanistic and thermodynamic understanding deepens [13, 16], the design of cocrystals will become even more predictable and effective. Pharmaceutical co-crystallization is no longer just an option for solubility enhancement; it is a robust, sophisticated, and indispensable tool in the modern pharmaceutical scientist's toolkit, poised to play a critical role in delivering the next generation of life-saving medicines.

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