

# Co-Former Selection and Optimization Strategies for Solubility Enhancement of Drugs: A Review

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## ABSTRACT

Poor aqueous solubility continues to hinder the development of many oral drug formulations, restricting both their bioavailability and therapeutic performance. One approach that has attracted increasing attention is co-crystallization, which can alter key physicochemical properties of a compound without changing its pharmacological profile. In this review, we examine how molecular docking and related computational methods can be used to guide the rational choice of co-formers in co-crystal design. Docking studies shed light on binding strength, hydrogen-bond preferences, and other intermolecular interactions, thereby helping to narrow down the pool of potential drug-co-former combinations. We highlight examples involving carboxylic acids, amino acids, and GRAS-listed co-formers, while also pointing out where computational predictions fall short of experimental outcomes, particularly due to limited co-former diversity. Experimental techniques such as PXRD, DSC, and SCXRD are considered alongside current regulatory guidance from the FDA and EMA, since both scientific feasibility and regulatory acceptance are critical to successful development. We conclude by discussing the need to combine docking with molecular dynamics, crystal structure prediction, and machine learning approaches, which together may yield more reliable predictions. Unlike earlier reviews that typically emphasize either computational or experimental perspectives, our aim is to integrate both, and to place them within the broader regulatory context, in order to provide a practical framework for co-former selection.

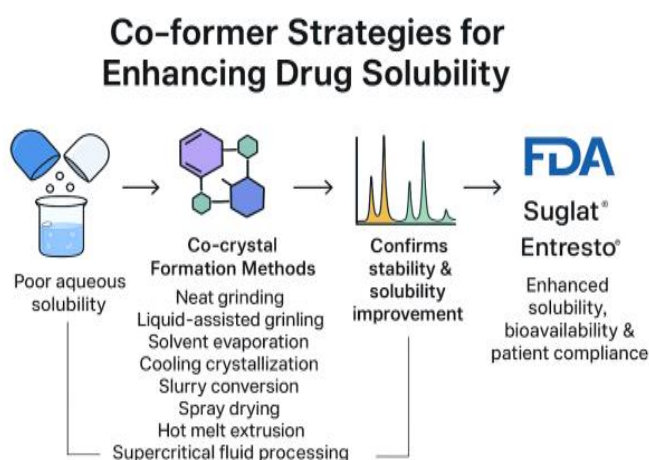
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**Graphical Abstract**



## 1. INTRODUCTION

Low aqueous solubility of the majority of active pharmaceutical molecules is among the greatest formulation development challenges. It is reported that about 40 % of drugs marketed, and about 90% of new chemical entities being developed, are either BCS Class II or Class IV drugs<sup>1</sup>. These drugs exhibit poor dissolution or permeability and becomes the rate-determining step for absorption. It is especially the case for drugs administered orally, as solubility has a significant influence on dissolution rate, absorption efficiency, therapeutic response, and pharmacokinetic properties<sup>2</sup>. Low-solubility drugs are usually likely to require higher doses during administration to attain therapeutic levels of plasma, which not only raises the risk of side effects and inter-patient difference but also adversely affects compliance in patients<sup>3</sup>. Hence, enhancing dissolution and solubility characteristics of APIs continues to be at the center of drug formulation research.

During the last two decades, there have been various formulation-based approaches that have been investigated to counter this issue. Salting out, reduction in particle size by micro particles or nanoparticles formation, solid dispersions, lipid-based drug delivery systems, and amorphous solid dispersions are some of the methods that have all met with varying levels of success<sup>4</sup>. Salt formation, for instance, is a traditional method but is limited to molecules containing ionizable functional groups<sup>5</sup>. Amorphous solid solutions will increase dissolution but are often limited by physical instability and a tendency to recrystallize over time<sup>6</sup>. Lipid-based drug delivery systems will enhance oral absorption but are difficult in both large-scale production and patient acceptance<sup>7</sup>. Therefore, while these traditional methods are still much valued, each has its own unique limitations regarding chemical compatibility, long-term stability, or industrial scale-up.

In this, drug co-crystals have also been often viewed as a viable option for changing the solid-state character of drug materials<sup>8</sup>. Co-crystals are crystalline solids that consist of more than one component, and these include a neutral co-

former and an API in a defined stoichiometric proportion, stabilized by non-covalent forces like hydrogen bonding,  $\pi$ - $\pi$  stacking, or van der Waals forces<sup>9</sup>. As opposed to salts, they are not dependent on the availability of ionizable groups in the drug and are therefore usable with a wider variety of APIs. Well-chosen co-formers allow co-crystals not only to improve solubility and dissolution rate, but permeability, stability, and even physical characteristics such as compressibility, without altering the drug's pharmacological activity<sup>10</sup>.

The majority of co-formers are also GRAS, further contributing to their acceptability for regulation (Childs et al., 2004). Successful marketing of products like Suglat® (ipragliflozin-L-proline cocrystal) and Entresto® (sacubitril/valsartan solid form) demonstrates their clinical and industrial relevance<sup>11</sup>. One of the key steps in co-crystal design is the identification of a suitable co-former. Historically, identification has relied on the empirical screening approach, wherein a series of crystallization experiments is prepared and analysed through means like powder X-ray diffraction and thermal analysis.

As effective as it is, the approach is labour-intensive, material-intensive, and time consuming. To simplify this, computational methods have been employed to predict and rank potential co-formers before experimentation. The molecular electrostatic potential mapping, hydrogen bond propensity scoring, and cambridge structural database analysis are helpful in approximating the likelihood of favourable supramolecular interactions<sup>12,13</sup>. Among these, molecular docking is a highly applicable technique providing information about binding affinity, hydrogen-bonding potential, and intermolecular geometry of co-former-drug pairs<sup>9,14</sup>. Because docking allows in-silico screening, it reduces the experimental burden and accelerates the discovery of probable co-crystals.

Current review articles have reported overall descriptions of pharmaceutical co-crystals with significant focus on their physicochemical advantages, regulatory implications, and experimental screening methods. Comprehensive reviews with specific regard to molecular docking and computational methods of co-former discovery are not

reported. This gap highlights the relevance of the present work, aiming to bridge computational strategies with experimental insights and regulatory perspectives in view of recent methodological advances in the field. In summary, present review emphasizes the potential of molecular docking as a rational and economical means to drive co-former selection. Through bridging the gap between in-silico prediction and laboratory confirmation, the present review aims to be an example of how computer-aided cocrystal design can produce formulations that are more soluble, more stable, and clinically superior performing. The majority of published review articles focus on experimental screening or physicochemical benefit of co-crystals. Computational approaches are typically mentioned in passing, and regulatory needs are typically excluded, although these are crucial for the translation into real-world products. In this article, we aimed to fill that gap and bring together molecular docking tools with experimental verification techniques and regulatory guidance to provide an integrated overview of co-former selection.

## 2. PRINCIPLES OF CO-FORMER SELECTION

Pharmaceutical co-crystal design is based upon the principles of supramolecular chemistry, wherein non-covalent interactions are used to determine predictable assembly of the molecules<sup>8,15</sup>. The API needs to be capable of interaction with a well-chosen co-former with favourable molecular interactions to form a stable co-crystal. The process is not random; it requires a careful evaluation of molecular compatibility, physicochemical characteristics, and regulatory relevance. A set of directing principles is applied in the selection process, each enhancing the possibility of reaching a pharmaceutically acceptable and functionally desired co-crystal, as shown in Figure 1.

### 2.1 Supramolecular Synthons and Intermolecular Interactions

The concept of supramolecular synthons lies at the core of co-crystal formation. There are repeated structural units connected through non-covalent interactions, most commonly hydrogen bonds<sup>16</sup>. In pharmaceutical

applications, two principal classes of synthons are typically recognized.

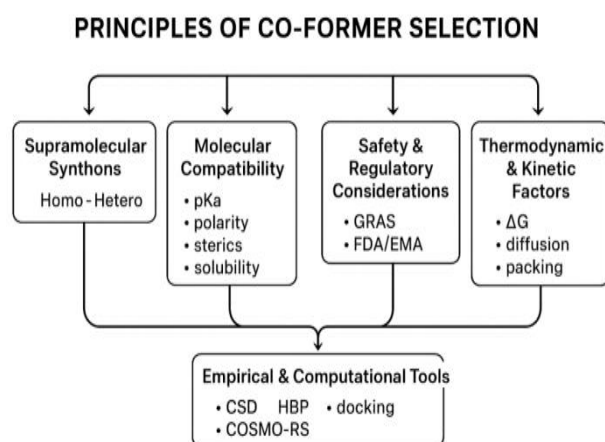


Figure 1: Principles of Co-former Selection

Homomeric synthons are formed between two identical functional groups, such as the dimerization of two carboxylic acids<sup>17</sup>, whereas heteromeric synthons arise from complementary functional groups, for example, carboxylic acid–amide or amide–pyridine hydrogen bonds<sup>18</sup>. APIs with hydrogen bond donors and acceptors (e.g., –OH, –COOH, –NH<sub>2</sub>, –C=O, –N=) are suitable for co-crystallization<sup>19,20</sup>. For example, carboxylic acid functional groups readily form stable heterosynthons with pyridines or amides, while hydroxyl and carbonyl groups form stable donor–acceptor interactions<sup>18</sup>. The predictability and stability of such supramolecular synthons can increasingly be assessed by computational chemistry and molecular docking, providing insight into spatial arrangements and binding energetics of API–co-former complexes.

### 2.2 Molecular Compatibility

The suitability of a co-former is largely determined by the extent to which its physicochemical properties are compatible with those of the drug molecule<sup>21</sup>. Several parameters are typically considered in this context. Polarity and hydrogen-bonding capability play a crucial role, as highly dipolar and hydrogen-bonding molecules tend to form more stable co-crystals<sup>22</sup>. Differences in pKa values, although less critical for salt formation, can still influence co-crystal stability, with minor variations between the drug and co-former often resulting in stronger non-covalent interactions. Steric size and geometry are also important, since good steric compatibility facilitates effective packing

within the crystal lattice. In addition, the relative solubility of the co-former can significantly impact the dissolution behaviour of the resulting co-crystal, with more soluble co-formers generally enhancing dissolution. Commonly used co-formers such as nicotinamide and saccharin are examples of these properties; their ability for strong hydrogen-bonding and high aqueous solubility are significant contributors to dissolution improvement of weakly soluble APIs<sup>23</sup>.

### 2.3 Safety and Regulatory Consideration

Apart from molecular compatibility, regulatory approval and safety profile of a co-former are also important. Regulatory agencies like the U.S. FDA and the EMA recognize co-crystals as a unique crystalline phase of APIs, provided the co-former is pharmaceutically acceptable<sup>24</sup>. With an attempt to aid approval processes, the majority of researchers employ GRAS co-formers or those with a known toxicology profile<sup>25</sup>.

Examples of GRAS co-formers that have been regulated include succinic acid, citric acid, fumaric acid, malic acid, and tartaric acid<sup>26</sup>. Regulation approval of such co-formers has enabled the market approval of such products as entrectinib–fumaric acid co-crystal and sacubitril–valsartan co-crystal, demonstrating the commercial potential for this approach<sup>27,28</sup>. Hence, selection of co-formers is equally a matter of regulatory caution as molecular design.

### 2.4 Thermodynamic and Kinetic Considerations

The success of co-crystal formation is influenced by both thermodynamic and kinetic factors<sup>29</sup>. From a thermodynamic view, the lattice free energy of the co-crystal must be lower than that of the individual drug and co-former, a condition that ensures greater stability. Computational tools such as molecular docking and lattice energy calculations are often employed to predict this stability<sup>30,31</sup>. However, thermodynamic favourability alone does not guarantee co-crystal formation. Kinetic viability also plays a critical role, as the process requires feasible pathways for molecular diffusion and interaction. If these kinetic conditions are not met, a thermodynamically stable cocrystal may still fail to form under experimental conditions. Existing computational advancements allow researchers to consider such factors in advance, thereby

reducing dependence on large-scale experimental trials<sup>32</sup>.

### 2.5 Empirical and Computational Principles

A variety of empirical and computational models have been developed to predict the likelihood of successful co-crystal formation. Hydrogen Bond Propensity (HBP) models are commonly used to statistically assess whether a drug is more likely to self-associate or interact with a co-former<sup>33</sup>. Analysis of the Cambridge Structural Database (CSD) provides insights into frequently observed supramolecular units and well-established synthons, guiding rational co-former selection. Molecular docking techniques further enable the estimation of binding affinity, hydrogen-bond distances, and interaction energies, allowing for prioritising of potential co-formers<sup>9</sup>. Additionally, lattice energy calculations and COSMO-RS modelling offer predictions of thermodynamic stability and solubility behavior, enhancing the reliability of *in silico* co-former screening and complementing empirical observations. By combining these empirical rules with advanced computational resources, researchers can significantly accelerate the process of choosing co-formers, minimizing trial-and-error and increasing the potential of the attainment of stable, pharmaceutically interesting co-crystals.

## 3. COMPUTATIONAL CO-FORMER SCREENING METHODS

Computational co-former screening methods are most effective when integrated with experimental validation and consideration of regulatory requirements. By coupling *in silico* predictions with laboratory analysis, these approaches not only enhance the accuracy of co-former selection but also ensure that the results are practically relevant and clinically applicable. The advent of computational approaches has transformed co-former selection by reducing dependence on time and resources. Intensive experimental screening tools such as AutoDock, DockThor, GOLD, and SwissDock facilitate systematic evaluation of multiple conformations and the ranking of co-formers based on their estimated binding energies, with lower (more negative) values indicating stronger, more stable interactions<sup>34</sup>. Binding energy, expressed as the change in free energy ( $\Delta G$ ) upon complex formation, reflects the strength of the

interaction between the drug and co-former<sup>35</sup>. A useful analogy is to consider the drug and co-former as puzzle pieces: the better they fit together, the more energy is released, resulting in a more stable complex. By integrating in-silico predictions with experimental validation and regulatory considerations, these computational approaches not only streamline co-former selection but also ensure that the outcomes are practically relevant and clinically applicable.

Beyond binding energy calculations, additional approaches help predict the likelihood and nature of co-crystal formation. Docking is often complemented by molecular electrostatic potential (MEP) mapping, which enables the localization of electron-rich and electron-deficient regions of a molecule and anticipates favourable donor–acceptor interactions<sup>36</sup>. For instance, carbonyl oxygen atoms in carboxylic acids are very electronegative and are inclined towards interacting with electron-deficient hydrogen of amides or hydroxyls. Similarly, hydrogen bond propensity (HBP) scoring, supported by CSD evidence, offers statistical tools for prediction of whether drug–co-former interaction will dominate over drug–drug interaction<sup>37</sup>.

Though helpful, docking protocols are not without limitations. Scoring functions vary between different software packages and do not always reflect experimental results. Most computational protocols also ignore solvent effects and the kinetics of crystallization, which are important in real systems. Docking provides only a static view of molecular interactions without considering phenomena such as polymorphism or dynamic crystal packing. Accordingly, some theoretically anticipated drug–co-former pairs with high affinity may not yield stable co-crystals experimentally<sup>38</sup>.

Computational approaches based on docking and enhanced by complementary methods have become valuable tools for rational co-former screening. This predictive tool, when combined with experimental validation, enables more efficient and targeted co-crystal development. Workflow of docking guided co-former selection is given in Figure 2.

To address these limitations, researchers increasingly combine docking with molecular dynamics (MD), lattice

energy calculations, and crystal structure prediction (CSP) increasingly<sup>39</sup>. These methods account for solvent effect, dynamic movement, and packing efficiency, thereby providing a more integrated assessment of the viability of cocrystal.

Emerging approaches are exploring the use of machine learning (ML) and artificial intelligence (AI), which apply large datasets of reported co-crystals to predict new, non-intuitive co-formers based on docking studies<sup>40</sup>. However, the lack of standardized docking protocols remains a challenge, as methodological differences make it difficult to reproduce results or compare findings across studies.

Future progress in this area will depend on the harmonization of workflows, the expansion of chemical libraries beyond traditional GRAS-listed molecules, and the systematic verification of predictions through carefully designed experimental studies.

### Workflow of Docking-Guided Co-former Selection

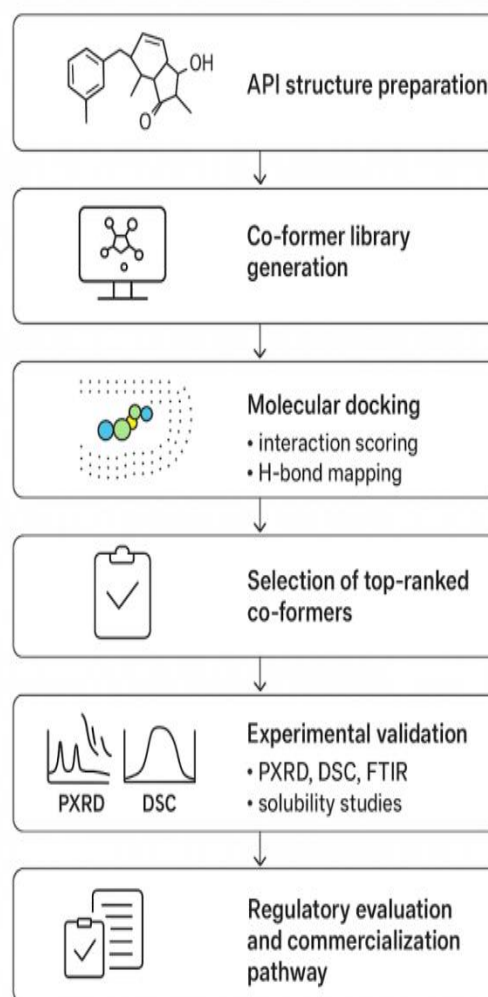


Figure 2: Workflow of Docking Guided Co-former Selection

#### 4. PHARMACEUTICAL CO-CRYSTALLIZATION CASE STUDIES OF CO-FORMERS

Pharmaceutical co-crystallization case studies highlight the effectiveness of amino acids and carboxylic acids as rationally designed co-formers, as shown in Table 1. Predictions from docking studies, when supported by experimentation, have demonstrated their dominant role in enhancing solubility and bioavailability of drugs. Amino acids and carboxylic acids are widely utilized due to their multiple hydrogen bond donor and acceptor sites, structural diversity, and favourable safety profile<sup>41</sup>. The zwitterionic nature of amino acids further enables them to generate stable supramolecular synthons with active pharmaceutical ingredients (APIs). Several of these molecules are also classified as generally recognized as safe (GRAS), minimizing toxicological concerns and facilitating translation into clinically acceptable formulations.

Examples include glycine, which forms co-crystals with carbamazepine and theophylline, leading to faster dissolution rates; L-tryptophan, which improves solubility

and stability through hydrogen bonding and  $\pi$ - $\pi$  stacking interactions; and L-proline, which is part of the marketed cocrystal drug Suglat® (ipragliflozin-L-proline), confirming clinical and regulatory relevance<sup>34,42</sup>. Similarly, aspartic acid enhances the crystallinity and solubility of carbamazepine. Among carboxylic acids, fumaric acid, succinic acid, oxalic acid, and malonic acid have been widely reported to form stable co-crystals with APIs such as indomethacin, ketoconazole, and acyclovir, showing marked improvements in solubility and dissolution<sup>43</sup>. Longer-chain acids like adipic and sebacic acid, and polyfunctional acids like tartaric acid, have also been successfully employed. Collectively, these case studies underscore the reliability of amino acids and carboxylic acids as efficient co-formers in cocrystal formulation. To ensure that these promising candidates deliver tangible pharmaceutical benefits, their computationally predicted performance must be validated through experimental confirmation

**Table 1.** Examples of amino acids and carboxylic acids used as co-formers in pharmaceutical co-crystals, with their functional features, drug pairings, and reported impact on solubility.

Co-former	Functional Traits	API Pairings	Observed Benefits
<b>Glycine</b>	Zwitterionic, H-bond donor/acceptor	Carbamazepine, Theophylline	Enhanced solubility, improved dissolution rate <sup>44</sup>
<b>L-Tryptophan</b>	Indole ring ( $\pi$ - $\pi$ stacking), H-bond donor/acceptor	Indomethacin, Naproxen	Increased solubility, dissolution, and lattice stability <sup>45</sup>
<b>L-Proline</b>	Cyclic amino acid, strong H-bond donor/acceptor	Ipragliflozin (Suglat®)	Marketed product; improved bioavailability, stability <sup>26</sup>
<b>Aspartic Acid</b>	Dicarboxylic side chain, multiple H-bonding possibilities	Carbamazepine	Improved solubility and crystallinity <sup>46</sup>
<b>Fumaric Acid</b>	Planar, strong dicarboxylic acid, predictable H-bonding	Carbamazepine, Indomethacin, Acyclovir	Stable lattice formation, significant solubility gain <sup>47</sup>
<b>Succinic Acid</b>	Flexible dicarboxylic acid, multiple donor/acceptor sites	Ketoconazole, Lamotrigine, Acyclovir	Improved solubility, enhanced dissolution <sup>48,49,50</sup>

Co-former	Functional Traits	API Pairings	Observed Benefits
<b>Oxalic Acid</b>	Short, strong dicarboxylic acid, high H-bonding ability	Theophylline, Fluoroquinolones	Faster dissolution, enhanced solubility <sup>51</sup>
<b>Malonic Acid</b>	Symmetrical, bidentate H-bond donor/acceptor	Acyclovir, Anti-tubercular agents	Improved stability and dissolution <sup>51</sup>
<b>Adipic Acid</b>	Long, flexible dicarboxylic acid	Acyclovir	Enhanced solubility, improved crystal packing <sup>51</sup>
<b>Tartaric Acid</b>	Multiple hydroxyl and carboxyl groups, strong H-bonding	Acyclovir, Diacerin	Improved dissolution, stable lattice <sup>51</sup>
<b>Sebacic Acid</b>	Long-chain dicarboxylic acid, flexible H-bond donor	Gliclazide	Enhanced solubility, better compressibility <sup>51</sup>

### 5. Experimental Optimization

In recent years, the search for suitable co-formers to enhance the solubility of poorly water-soluble drugs has driven the development of a wide range of experimental strategies as shown in Table 2. Traditional approaches such as neat grinding and liquid-assisted grinding remain popular for their ease and effectiveness, as they encourage solid-state interactions between drug and co-former molecules and often yield co-crystals with improved solubility<sup>9</sup>.

Solution-based techniques, including solvent evaporation, cooling crystallization, and slurry conversion, provide controlled conditions for systematic screening, enabling the identification of stable and reproducible co-crystal forms. At the same time, more advanced approaches such as antisolvent addition, spray drying, and supercritical fluid processing have proven highly effective for producing fine or nanosized particles with superior dissolution behavior. Hot melt extrusion has also gained considerable attention as a solvent-free and scalable method, particularly suited to industrial production due to its environmental and operational advantages. Together, these experimental methods represent a comprehensive toolkit for addressing the limitations of poorly soluble drugs, offering pathways to improve dissolution, bioavailability, and ultimately

therapeutic performance, while supporting both laboratory-scale investigations and large-scale pharmaceutical applications<sup>21</sup>.

**Table 2.** Experimental Methods for Co-Former Optimization and Solubility Enhancement of Poorly Water-Soluble Drugs.

Category	Method	Applications / Examples
Solid-state methods	Neat grinding	Early screening; e.g., carbamazepine co-crystals with nicotinamide
	Liquid-assisted grinding	APIs with limited solubility; e.g., indomethacin with saccharin
Solution-based methods	Solvent evaporation	Thermally stable drugs; e.g., caffeine–oxalic acid co-crystal
	Cooling crystallization	NSAIDs (ibuprofen, naproxen) for better solubility
	Slurry conversion	Screening stable salts/co-crystals; e.g., itraconazole formulations
Advanced methods	Antisolvent addition	Poorly soluble antifungals, e.g., griseofulvin
	Spray drying	Inhalable drugs and BCS Class II drugs (e.g., itraconazole spray-dried formulations)

Category	Method	Applications / Examples
	Supercritical fluid processing	Lipophilic drugs (e.g., paclitaxel, cyclosporine)
Thermal methods	Hot melt extrusion	Large-scale solid dispersions (e.g., ritonavir, posaconazole formulations)

## 6. REGULATORY, PATENT, AND COMMERCIAL PERSPECTIVES

The successful translation of pharmaceutical co-crystals from laboratory research to commercial products depends not only on scientific feasibility but also on regulatory clarity, intellectual property (IP) protection, and large-scale manufacturability. While molecular docking and experimental studies provide the scientific foundation, these additional considerations ultimately dictate clinical and market viability.

**Regulatory aspects:** Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) classify pharmaceutical co-crystals as distinct solid forms of active pharmaceutical ingredients (APIs)<sup>52</sup>. According to FDA guidance, co-crystals differ from salts, solvates, and polymorphs, as they consist of neutral co-formers linked to APIs through non-ionic interactions such as hydrogen bonding. Regulatory pathways are simplified when the co-former is already classified as Generally Recognized as Safe (GRAS) or previously approved for pharmaceutical use, making amino acids (e.g., glycine, L-proline, tryptophan) and carboxylic acids (e.g., fumaric acid, succinic acid) especially attractive candidates. EMA regulations additionally emphasize thorough characterization including solubility, stability, dissolution, and pharmacokinetics before approval<sup>53</sup>.

**Intellectual property:** Co-crystals offer significant opportunities for new patents because they are regarded as novel solid-state forms of APIs. If they demonstrate improved solubility, stability, or bioavailability, they can be

patented independently from the parent drug<sup>54</sup>. This makes co-crystals a strategic approach to extending product life cycles for drugs nearing patent expiry. Numerous patents have been filed for amino acid and carboxylic acid based co-crystals, typically supported by PXRD or SCXRD data and experimental evidence of enhanced pharmaceutical performance. The marketed co-crystal-based products are given in Table 3.

**Commercial aspects:** For clinical and regulatory acceptance, co-crystals must be manufactured reproducibly in high yield and purity at scale, often using methods such as solution crystallization, solvent evaporation, grinding, or spray drying. Compliance with Good Manufacturing Practice (GMP) is essential for ensuring quality and reproducibility. Successful marketed examples such as Entresto® (sacubitril–valsartan) and Suglat® (ipragliflozin–L-proline) demonstrate that these requirements can be met<sup>11</sup>. The widespread use of amino acids and carboxylic acids in commercial co-crystals highlights their feasibility and safety.

**Challenges:** Despite progress, regulatory definitions of co-crystals continue to evolve, occasionally confusing differences with salts and polymorphs. Moreover, while docking predicts strong drug–co-former interactions, it cannot account for large-scale producibility, long-term stability, or industrial scalability, all of which must be determined experimentally. Patent disputes are also common when multiple groups investigate similar API–co-former systems.

The path to commercialization requires a balance of regulatory approval, patentability, and manufacturability, alongside computational and experimental validation. The use of GRAS-listed amino acids and carboxylic acids provides both scientific and regulatory advantages, making them leading candidates for clinically viable co-crystal formulations. By integrating regulatory, patent, and industrial perspectives with scientific advances, future efforts can more effectively guide both academic research and pharmaceutical innovation.

**Table 3.** Marketed, approved, and investigational co-crystal based pharmaceutical products, including their APIs, co-formers, therapeutic indications, approval status, and clinical development stage.

Product	API(s)	Co-former	Indication	Approval
Suglat®	Ipragliflozin	L-Proline (amino acid)	Type 2 Diabetes	2014, Japan (PMDA approval) <sup>55</sup>
Steglatro®	Ertugliflozin	L-Pyroglutamic acid	Type 2 Diabetes	2017, FDA (U.S.) <sup>56</sup>
Lexapro®	Escitalopram oxalate	Oxalic acid	Anxiety and Depression	2002, FDA (U.S.) <sup>57</sup>
Dimenhydrinate	Diphenhydramine 8 chlorotheophylline	(ion-exchange solid form)	Motion sickness	1952, FDA (U.S.) <sup>58</sup>

## 7. CONCLUSION

Molecular docking has emerged as an effective computational tool to guide co-former selection in pharmaceutical cocrystallization. By anticipating interactions, binding affinities, and structural compatibility, it provides a rational and economical alternative to trial-and-error screening for improving solubility, dissolution, and stability of poorly soluble drugs.

Moreover, limitations remain, including overgeneralized scoring functions, inadequate treatment of solvent and kinetic effects, and the absence of standardized protocols. While case studies confirm the feasibility of docking-guided co-crystals, they also highlight gaps in scalability, manufacturability, and the diversity of applicable co-formers.

Future progress will depend on combining docking with complementary computational methods such as molecular dynamics, free-energy calculations, and crystal structure prediction alongside AI and ML to enhance predictability. Equally essential is rigorous experimental validation using PXRD, SCXRD, DSC, and dissolution studies, and stronger integration with regulatory science.

The success of commercial products demonstrates that co-crystals can reach the market when scientific, regulatory, and manufacturing challenges are aligned. Going forward, the convergence of computational prediction, experimental

validation, and regulatory acceptance offers a practical pathway to make co-crystals a typical strategy for enhancing drug bioavailability and therapeutic performance.

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