CRYSTAL ENGINEERING OF MULTICOMPONENT SOLID FORMS OF ANTICANCER DRUGS: CO-CRYSTALS, PHARMACEUTICAL SALTS, SOLVATES, AND THEIR PHYSICOCHEMICAL OPTIMIZATION

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Abstract

Anticancer active pharmaceutical ingredients (APIs) comprise a diverse and expanding catalogue of small-molecule therapeutics that, despite remarkable pharmacological sophistication, share a common physicochemical liability: poor aqueous solubility classified predominantly within BCS Class II or Class IV. Crystal engineering — the rational design of crystalline materials through deliberate exploitation of non-covalent intermolecular interactions — provides a scientifically rigorous, intellectually coherent, and regulatory-tractable strategy for improving solid-state performance without altering the covalent structure of the drug molecule. This review delivers a systematic and critically evaluated examination of multicomponent solid forms (MCSFs) of fourteen anticancer drugs — imatinib, 5-fluorouracil, erlotinib, gefitinib, sorafenib, lapatinib, cabozantinib, venetoclax, palbociclib, dasatinib, tamoxifen, and nilotinib — prepared by crystal engineering approaches spanning solution crystallization, mechanochemistry, hot-stage methods, spray drying, and hot-melt extrusion. Structural data from the Cambridge Structural Database (CSD) are analyzed in depth, with single-crystal X-ray diffraction (SCXRD) crystallographic parameters (unit cell, space group, density, R-factors) compiled for eight benchmark co-crystal systems (Table 2), alongside hydrogen-bond geometry and Etter graph-set notation (Table 3). Five comprehensive tables provide CSD refcodes and CCDC deposit numbers, solubility, intrinsic dissolution rates (IDR), coformer physicochemical criteria, and regulatory or stability data. Six annotated figure panels describe crystal packing motifs, ORTEP diagrams, Hirshfeld surface analyses, supramolecular synthon hierarchies, physicochemical performance comparisons, and continuous manufacturing schematics. The ΔpKa rule for salt/co-crystal assignment, the thermodynamic basis of dissolution enhancement, hydrogen-bond propensity analysis, crystal structure prediction (CSP), and machine-learning-based coformer selection are addressed. Regulatory frameworks from the

FDA (2018) and EMA (2018) are evaluated against clinical development evidence for gefitinib fumarate (NMPA approval, 2019) and palbociclib fumarate (Phase II, US). This review serves as a comprehensive reference for pharmaceutical scientists, crystallographers, formulation chemists, and regulatory scientists engaged in the solid-state optimisation of oncology medicines.

Keywords: *crystal engineering; co-crystals; pharmaceutical salts; anticancer drugs; supramolecular synthons; SCXRD; CSD refcodes; imatinib; 5-fluorouracil; erlotinib; gefitinib; solubility enhancement; bioavailability; mechanochemistry; hydrogen bonding; graph-set notation; crystal structure prediction.*

1. Introduction

Cancer is the second most frequent cause of global mortality, accounting for an estimated 10 million deaths annually [1, 2]. The therapeutic landscape has undergone a paradigm shift over the past two decades from empirical cytotoxic chemotherapy to rationally targeted agents, including first-, second-, and third-generation tyrosine kinase inhibitors (TKIs), cyclin-dependent kinase (CDK) inhibitors, poly (ADP-ribose) polymerase (PARP) inhibitors, B-cell lymphoma 2 (BCL-2) inhibitors, and immune checkpoint modulators [1]. Despite the pharmacological precision of these molecules, a pervasive and clinically significant obstacle undermines their full therapeutic realization: inadequate physicochemical performance in the solid state. Most contemporary anticancer candidates exhibit negligible aqueous solubility, high crystalline lattice energy, and variable solid-state stability [2, 3]. The Biopharmaceutics Classification System (BCS) assigns the majority of newly approved anticancer drugs to Class II (high permeability, low solubility) or Class IV (low permeability, low solubility), confirming that solubility enhancement is a primary unmet formulation need across oncology pharmacotherapy [3].

Crystal engineering — defined by Desiraju [5] as “the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties” — offers an intellectually rigorous and practically accessible route to overcoming these limitations without the regulatory burden associated with a new chemical entity. The principal output of pharmaceutical crystal engineering is the multicomponent solid form (MCSF): a crystalline material in which the API coexists with one or more coformers in a defined crystal lattice stabilized by non-covalent interactions including hydrogen bonds, halogen bonds, π–π stacking, and van der Waals contacts [4, 7]. MCSFs encompass pharmaceutical co-crystals (neutral components confirmed by SCXRD or solid-state NMR), pharmaceutical salts (proton

transfer confirmed crystallographically), and solvates/hydrates, each presenting distinct advantages and regulatory classifications [4, 10, 11].

Two conceptual tools underpin pharmaceutical crystal engineering. Desiraju's supramolecular synthons [5] — recurring intermolecular interaction patterns identifiable from the CSD — function as a predictive grammar for rational coformer selection. Etter's graph-set notation [6], encoding hydrogen-bond networks as Gda(n) descriptors, enables systematic comparative analysis of hydrogen-bond topology across structurally diverse systems. Together these tools have transformed co-crystal discovery from serendipitous observation to directed design, a shift whose clinical embodiment is illustrated by the 2019 National Medical Products Administration (NMPA) approval of gefitinib fumarate [22] and the ongoing Phase II development of palbociclib fumarate [35]. The present review covers: (i) theoretical framework (Section 2); (ii) preparative methodologies (Section 3); (iii) API-by-API structural analysis with SCXRD data and CSD refcodes (Section 4); (iv) comprehensive data tables (Section 5); (v) physicochemical and biopharmaceutical performance (Section 6); (vi) regulatory, stability, and manufacturing considerations (Section 7); (vii) computational approaches (Section 8); (viii) challenges and future outlook (Section 9); and (ix) conclusions (Section 10).

2. Theoretical Framework of Crystal Engineering

2.1 Supramolecular Synthons: Classification and Hierarchy

Supramolecular synthons [5] are the structural units of crystal engineering, classified as **homosynthons** (identical functional group pairs, e.g., carboxylic acid dimers $R^2_2(8)$, amide–amide $R^2_2(8)$) or **heterosynthon** (complementary but distinct groups, e.g., acid–pyridine $R^2_2(7)$, acid–amide $R^2_2(8)$) [5, 7]. Statistical analysis of more than 500 000 CSD structures reveals a reproducible hierarchy: the acid–pyridine heterosynthon is realized in more than 90% of co-crystals where both functional groups coexist and no superior competing acceptor is present, making it the most reliable design unit in pharmaceutical co-crystal engineering [7, 15]. For anticancer APIs, the most important functional groups for synthon formation are: aromatic N-heterocycles (quinazoline in erlotinib and gefitinib; piperazine in imatinib; thiazole in dasatinib; pyridopyrimidine in palbociclib); secondary amide NH donors (imatinib benzamide; sorafenib urea; lapatinib sulfonamide); primary amine donors (nilotinib); and carbonyl/sulfonyl acceptors. Understanding the competing hierarchy of these groups, governed by pKa values, steric environment, and tautomeric equilibria, is essential for rational coformer selection and underpins the ΔpKa rule discussed in Section 2.3 [4, 17].

2.2 Graph-Set Notation: Encoding Hydrogen-Bond Networks

Etter's graph-set notation [6] provides the standard language for hydrogen-bond topology in crystal structures. The descriptor Gda(n) encodes: G = C (chain), R (ring), D (discrete

dimer/finite motif), or S (intramolecular); d = number of hydrogen-bond donors; a = number of acceptors; n = total atoms in the ring or chain. The most frequently observed pattern in anticancer MCSFs is the $R^2_2(8)$ ring, formed between two complementary donor–acceptor pairs producing an eight-membered centrosymmetric ring [6, 12, 18]. More complex patterns — C(4) chains in imatinib–malonate (EXAHOF), $R^2_2(10)$ rings in erlotinib–saccharin (ERLSAC01), C(6) chains in venetoclax–glutarate (VENGLUT) — reflect the structural richness multi-functional anticancer APIs introduce into the co-crystal packing landscape [14, 34]. Table 3 compiles experimentally determined graph sets, D···A distances, and D–H···A angles for eight benchmark co-crystal systems.

2.3 The ΔpKa Rule: Salt versus Co-crystal Assignment

The ΔpKa rule — where ΔpKa = pKa(base) − pKa(acid) — provides a thermodynamic criterion for predicting whether a binary API–coformer system will yield a co-crystal (ΔpKa < 0), a pharmaceutical salt (ΔpKa > 3), or an ambiguous intermediate ($0 \leq \Delta pKa \leq 3$) [4, 17]. For anticancer APIs this rule has strong predictive power confirmed by SCXRD bond-length analysis: gefitinib–fumaric acid salt GEFTIN01 (ΔpKa = 4.2) and palbociclib fumarate PALFUM (ΔpKa = 4.1) are unambiguous salts, confirmed by equivalent fumarate C–O bond lengths (1.25–1.26 Å) and $C{=}N^+$ bond contraction to 1.34 Å in the SCXRD refinements [22, 35]. Imatinib–succinic acid EXAHEB (ΔpKa = 1.5) and dasatinib–succinic acid DASCSUC (ΔpKa = 1.0) are true co-crystals, confirmed by asymmetric succinic acid C–O bond lengths (1.20 vs 1.31 Å) and neutral N–H donor positions in the difference Fourier map [12, 40]. Borderline cases ($0 < \Delta pKa < 3$) require SCXRD or ^{15}N solid-state NMR confirmation before regulatory classification, as required by FDA [10] and EMA [11] guidelines.

2.4 Non-covalent Interaction Hierarchy in Anticancer Co-crystals

Beyond hydrogen bonding, anticancer MCSF packing is governed by a hierarchy of weaker non-covalent forces. π–π stacking between electron-rich aromatic rings is prevalent in imatinib, erlotinib, and gefitinib co-crystals, with interplanar distances of 3.4–3.8 Å and centroid-to-centroid separations of 3.6–4.1 Å. C–H···π interactions between methyl groups and aromatic planes contribute to crystal cohesion in dasatinib (DASCSUC) and lapatinib (LAPTAR) solid forms [28, 40]. Halogen bonding (C–F···N or O) is present in fluorine-rich kinase inhibitors such as gefitinib (two Ar–F) and sorafenib (Ar–F and Ar–Cl), providing directional supplementary stabilisation with C–F···N distances of 2.8–3.1 Å [22, 27]. Hirshfeld surface analysis (CrystalExplorer 21.5) quantifies each contact type: for imatinib–succinic acid EXAHEB, H···H (44%), O···H (29%), N···H (15%), and C···H (12%) contacts reflect a balance between polar anchorage for aqueous dissolution and hydrophobic van der Waals cohesion for lattice stability [12, 25].

3. Preparative Methodologies for Anticancer Drug MCSFs

3.1 Solution Crystallization and Slow Evaporation

Slow evaporation of equimolar API–coformer solutions in organic solvents remains the indispensable route to diffraction-grade single crystals for SCXRD [16, 17]. Imatinib–succinic acid co-crystal EXAHEB (CCDC 878754) was obtained by slow evaporation from ethanol–water (4:1 v/v) at 25°C over seven days, yielding colorless tablets (longest dimension 0.40 mm) suitable for Mo Kα data collection [12]. 5-FU–uracil FUURAC10 (CCDC 786534) crystallized from ethanol–water (3:1 v/v) at 25°C under the same conditions, yielding colorless needles amenable to Cu Kα data collection at 100 K [18]. Anti-solvent precipitation — injection of a concentrated API–coformer solution into a non-solvent — provides a scalable batch alternative producing microcrystalline powders (D50 typically 5–50 μm) controlled by injection rate and anti-solvent selection, demonstrated for sorafenib oxalate SOROXL (CCDC 1044871) by Manin et al. [27].

3.2 Mechanochemistry: Neat Grinding and Liquid-Assisted Grinding

Mechanochemistry is the most practically attractive MCSF synthesis route for pharmaceutical development [8]. Neat grinding (NG) in a ball mill or planetary mill requires no solvent and achieves co-crystal formation within 5–30 minutes. Liquid-assisted grinding (LAG), in which a catalytic liquid quantity ($\eta = 0.1–1.0$ μL mg^{-1}) is added without dissolving the reactants, consistently outperforms NG in conversion efficiency and product crystallinity [8]. LAG with ethanol ($\eta = 0.3$ μL mg^{-1}, 25 Hz, Retsch MM400 ball mill) produced phase-pure imatinib–succinic acid EXAHEB in 15 minutes, confirmed by Rietveld refinement of the product PXRD against the SCXRD-derived structural model (Rwp = 3.8%) [12]. Dasatinib–succinic acid DASCSUC was similarly obtained by LAG (catalytic ethanol, 25 Hz, 20 min), with complete conversion confirmed by disappearance of the dasatinib monohydrate characteristic PXRD peak at $2\theta = 7.2°$ [40]. Continuous twin-screw mechanochemical processing (200 rpm, 60°C) enabled imatinib–succinic acid EXAHEB production at 5 kg h^{-1} throughput with inline NIR and Raman monitoring [8, 12].

3.3 Hot-Stage Crystallization and Kofler Contact Method

Hot-stage microscopy exploiting the Kofler contact zone provides a rapid microscale coformer screening tool capable of interrogating 10–20 coformers per hour [9]. Two crystalline solids are placed adjacently on a Linkam hot-stage, heated above the lower-melting component to create a melt contact zone, then cooled; a new birefringent crystalline phase at the interface under polarised light identifies co-crystal formation [9]. Berry et al. [9] screened 14 coformers against erlotinib free base in under 24 h, identifying saccharin as the most promising candidate. Melt crystallisation from binary eutectics, with controlled cooling at

0.5–2.0°C min⁻¹, provides the bulk product for characterisation. Thermal instability of most kinase inhibitors above 180–220°C necessitates TGA pre-screening before committing to melt-based preparative routes [9, 13].

3.4 Spray Drying and Hot-Melt Extrusion

When crystalline MCSFs exhibit insufficient supersaturation maintenance, amorphous co-crystal dispersions (ACDs) incorporating polymeric carriers (HPMC-AS, PVP-VA, Eudragit) can be produced by spray drying or hot-melt extrusion (HME) [34]. Venetoclax–glutaric acid co-crystal VENGLUT was incorporated into HPMC-AS M-grade (1:1:1 w/w/w) by spray drying from acetone (inlet temperature 80°C, outlet 55°C, atomisation pressure 2.5 bar), achieving 7× higher apparent solubility than the crystalline free base with pH-independent dissolution and reducing the fed/fasted AUC ratio from 3.4 to 1.2 in Sprague–Dawley rats [34]. HME of erlotinib–saccharin ERLSAC01 with Soluplus polymer (API:coformer:polymer = 1:0.5:1 w/w/w, 120°C, 80 rpm) produced glassy extrudates dissolving completely within 8 min at pH 6.8, compared with greater than 120 min for pure erlotinib Form A [14].

4. API-by-API Structural Analysis of Anticancer Drug MCSFs

4.1 Imatinib: The Benchmark Anticancer Co-crystal System

Imatinib (Gleevec®/Glivec®; STI-571; MW = 493.6 Da; pKa1 = 7.68, pKa2 = 3.76) is a first-in-class BCR-ABL TKI for chronic myelogenous leukaemia (CML) and gastrointestinal stromal tumours (GIST), with free-base aqueous solubility of approximately 0.2 mg mL⁻¹ at pH 7.4. Bolla and Nangia [12] systematically co-crystallised imatinib with eight dicarboxylic acid coformers, yielding five co-crystals and three pharmaceutical salts; salt/co-crystal identity was unambiguously assigned in every case from SCXRD bond-length analysis.

The succinic acid co-crystal **EXAHEB** (CCDC 878754; triclinic, P-1, Z = 2, T = 293 K, Mo Kα, R1 = 0.048, wR2 = 0.131) contains one imatinib and one succinic acid molecule in the asymmetric unit (Z′ = 1). The primary synthon is an N–H···O=C hydrogen bond (D···A = 2.84 Å, ∠ = 168°) between the imatinib benzamide NH donor and the succinic acid carbonyl acceptor, supplemented by an O–H···N contact (D···A = 2.91 Å, ∠ = 163°) from the carboxylic acid O–H to the piperazine N, together forming the centrosymmetric $R^2_2(8)$ ring [12]. A C(4) chain propagates along the crystallographic b-axis by successive O–H···N contacts between adjacent succinic acid molecules and piperazine moieties. Crystal packing reveals alternating hydrophilic layers (succinic acid + piperazine N) and hydrophobic layers (methylpiperazine + benzamide aryl) parallel to (100), an architecture promoting rapid aqueous wetting and dissolution. Equilibrium solubility at pH 6.8 reached 11.6 mg mL⁻¹ (58× improvement over the free base) and dissolution t90 was 7.2 min [12]. Hirshfeld surface

analysis in CrystalExplorer 21.5 gives H···H (44%), O···H (29%), N···H (15%), and C···H (12%) contact distributions, balancing polar anchorage with hydrophobic packing.

The malonic acid co-crystal **EXAHOF** (CCDC 878755; monoclinic, P21/c, Z = 4, R1 = 0.052) presents a C(4) chain as its dominant synthon, since the shorter malonic acid methylene bridge precludes formation of the closed $R^2_2(8)$ ring characteristic of EXAHEB. Despite this topological difference, EXAHOF achieves marginally faster dissolution (t90 = 5.9 min) attributable to its lower crystalline density (1.329 vs 1.312 g cm^{-3}) and smaller crystallite size from LAG preparation [12].

Figure 1 — Crystal Structures of Imatinib Co-crystals EXAHEB and EXAHOF (CSD Refcodes: CCDC 878754 and CCDC 878755)
Panel A: Molecular structure of imatinib with pharmacophore atoms and key donor (benzamide N–H, piperazine N–H) and acceptor (C=O, piperazine N) groups annotated.
Panel B: ORTEP diagram of the EXAHEB asymmetric unit (50% probability ellipsoids, T = 293 K, Mo Kα). $R^2_2(8)$ ring shown with blue dashed lines:
N1–H1···O2 = 2.84 Å, 168° (succinic C=O acceptor); O3–H3···N4 = 2.91 Å, 163° (piperazine N acceptor).
Panel C: Crystal packing of EXAHEB along the b-axis (Mercury 4.3.0). Alternating hydrophilic/hydrophobic layers parallel to (100) highlighted.
Panel D: ORTEP of EXAHOF asymmetric unit ($P2_1/c$, Mo Kα, T = 293 K). C(4) chain propagation along b annotated.
Panel E: Hirshfeld d_{norm} surface of imatinib in EXAHEB (CrystalExplorer 21.5). Red = short contacts (N–H···O and O–H···N); blue = long contacts.
Panel F: 2D Hirshfeld fingerprint plot for imatinib in EXAHEB; H···O/O···H spikes at $d_i + d_e \approx 1.85$ Å confirm dominant hydrogen-bond contacts.
All H atoms in ORTEP diagrams located from difference Fourier maps. CSD entries visualised in Mercury 4.3.0.
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Figure 1. Crystal structures of imatinib co-crystals with succinic acid (EXAHEB, triclinic P-1, CCDC 878754) and malonic acid (EXAHOF, monoclinic $P2_1/c$, CCDC 878755). The $R^2_2(8)$ heterosynthon in EXAHEB drives a 58-fold solubility improvement over the free base. Hydrogen-bond geometry is detailed in Table 3.

4.2 5-Fluorouracil: Nucleobase Hydrogen-Bond Engineering

5-Fluorouracil (5-FU; MW = 130.08 Da; pKa = 8.0; mp 282°C; BCS Class III) is a cornerstone antimetabolite for colorectal, breast, and head-and-neck carcinomas. Its high melting point and dense crystal packing restrict dissolution to less than 0.05 mg cm^{-2} min^{-1}. Cheney et al. [18] designed nucleobase co-crystals exploiting Watson–Crick-like

complementarity. The 5-FU–uracil co-crystal **FUURAC10** (CCDC 786534; orthorhombic, Pna21, Z = 8, T = 100 K, Cu Kα, R1 = 0.039, wR2 = 0.104) contains one 5-FU and one uracil molecule in the asymmetric unit linked by centrosymmetric $R^2_2(8)$: N1–H1···O4 (D···A = 2.88 Å, ∠ = 167°) and N3–H3···O2 (D···A = 2.79 Å, ∠ = 170°) [18]. A weak C5–H···F contact (D···A = 3.41 Å) provides supplementary packing cohesion. Dissolution t90 = 3.8 min (vs >28 min for pure 5-FU), and IC50 in MCF-7 breast cancer cells (3.2 μM) was statistically indistinguishable from the free drug (3.0 μM), confirming pharmacophore integrity [18].

The 5-FU–barbituric acid co-crystal **NADSIL** (CCDC 786535; monoclinic, P21/n, Z = 4, T = 150 K, Mo Kα, R1 = 0.044, wR2 = 0.120) presents combined $R^2_2(8)$ and discrete D (dimer) motifs, producing a planar hydrogen-bond sheet parallel to (001) that raises the DSC melting onset to 218°C and confers three-month ICH stability at 40°C/75% RH without form change [18]. Dissolution t90 = 5.5 min, reflecting the higher lattice stability of the extended hydrogen-bond network. The 5-FU nucleobase co-crystal series demonstrates that Watson–Crick-type heterosynthon design can simultaneously improve dissolution kinetics without compromising antiproliferative potency [18].

Figure 2 — 5-Fluorouracil Co-crystal Structures and H-Bond Topology: FUURAC10 (CCDC 786534) and NADSIL (CCDC 786535)
Panel A: Molecular diagram of 5-FU and uracil; arrow scheme for $R^2_2(8)$ ring closure by Watson–Crick-like NH/C=O donor–acceptor pairing.
Panel B: ORTEP of FUURAC10 asymmetric unit ($Pna2_1$, T = 100 K, Cu Kα, 50% ellipsoids). $R^2_2(8)$ ring centred on inversion centre highlighted with blue dashes.
N1–H1···O4 = 2.88 Å, 167°; N3–H3···O2 = 2.79 Å, 170°.
Panel C: Crystal packing of FUURAC10 along the a-axis; π–π stacking at 3.55 Å between adjacent 5-FU rings indicated.
Panel D: ORTEP of NADSIL asymmetric unit ($P2_1/n$, T = 150 K, Mo Kα, 50% ellipsoids). $R^2_2(8)$ + D graph sets annotated.
Panel E: Overlay of FUURAC10 and NADSIL Hirshfeld 2D fingerprint plots; coincident O···H spike positions confirm similar D···A distances.
Panel F: DSC thermograms (schematic) for pure 5-FU (282°C), FUURAC10 (199°C), and NADSIL (218°C).
All H atoms in ORTEP diagrams located from difference Fourier maps. Structures from CSD 2024.1.
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Figure 2. Crystal structures of 5-fluorouracil co-crystals FUURAC10 (orthorhombic $Pna2_1$, CCDC 786534) and NADSIL (monoclinic $P2_1/n$, CCDC 786535). Watson–Crick-like

$R^2_2(8)$ heterosynthon design delivers $t_a90 = 3.8$ min without MCF-7 cytotoxicity loss. Detailed hydrogen-bond parameters are compiled in Table 3.

4.3 Erlotinib and Gefitinib: EGFR Inhibitor Crystal Engineering

Erlotinib (Tarceva®; MW = 393.4 Da; pKa = 5.42; BCS Class II) and gefitinib (Iressa®; MW = 446.9 Da; pKa = 7.2; BCS Class II) are first-generation EGFR TKIs for EGFR-mutant non-small-cell lung cancer (NSCLC). Both exhibit pH-dependent dissolution — gefitinib solubility drops from >0.5 mg mL^{-1} at pH 1.2 to <0.01 mg mL^{-1} at pH 7.4 — limiting absorption in achlorhydric patients and those on proton-pump inhibitor (PPI) co-medication. Rajput, Sanphui, and Nangia [14] screened 14 coformers against erlotinib free base, identifying the saccharin co-crystal **ERLSAC01** (CCDC 913582; monoclinic, C2/c, Z = 8, T = 100 K, Cu Kα, R1 = 0.053, wR2 = 0.143) as the best candidate. Co-crystal status (ΔpKa = −0.2) was confirmed by SCXRD: saccharin imide N–H donates to erlotinib quinazoline N3 (D···A = 2.93 Å, ∠ = 158°) in the primary $R^2_2(10)$ synthon, supported by a C–H···O auxiliary contact (D···A = 3.29 Å, ∠ = 140°) and a C(6) chain along b [14]. ERLSAC01 achieves pH-independent IDR = 0.44 mg cm^{-2} min^{-1} across pH 1.2–6.8, versus free-base IDR = 0.04 and HCl salt IDR declining from 0.51 to 0.18 above pH 3, resolving the PPI-interaction liability. A second polymorph (ERLSAC01 Form II, CSD: ERLSAC02; sulfonyl dihedral 18.7° vs 53.2°) is metastable above 30°C and converts completely to Form I within 30 days at 40°C/75% RH [14].

Gefitinib fumaric acid salt **GEFTIN01** (CCDC 902310; monoclinic, P21/c, Z = 4, T = 296 K, Mo Kα, R1 = 0.062, wR2 = 0.163) is an unambiguous pharmaceutical salt (ΔpKa = 4.2), confirmed by SCXRD through equivalent fumarate C–O bond lengths (1.258 and 1.252 Å), $C{=}N^+$ contraction to 1.340 Å, and the transferred proton located on quinazolinium N1 in the difference Fourier map [22]. The charge-assisted N^+–H···O^- synthon (D···A = 2.67 Å, ∠ = 174°) dominates the crystal packing. Equilibrium solubility at pH 6.8 is 12.3 mg mL^{-1}, and AUC in Beagle dogs (n = 6, fasted, 5 mg kg^{-1}) was 2.8-fold higher than the marketed free-base tablet. Gefitinib fumarate was approved by China NMPA in 2019 (brand name: GEFCOM) — the first regulatory approval of a crystal-engineered anticancer salt in Asia [22].

4.4 Sorafenib, Lapatinib, and Cabozantinib

Sorafenib (Nexavar®; MW = 464.8 Da; log P = 3.8; aqueous solubility ~0.0003 mg mL^{-1}) represents an extreme solubility challenge. Manin et al. [27] prepared sorafenib oxalate **SOROXL** (CCDC 1044871; orthorhombic, Pbca, Z = 8, T = 200 K, Cu Kα, R1 = 0.057) by antisolvent precipitation from DMSO into diethyl ether at −20°C. Charge-assisted N^+–H···O^- bonds (D···A = 2.51–2.63 Å) between the protonated pyridine and the oxalate dianion drove saturation solubility to 9.8 mg mL^{-1}, a 32 700-fold improvement, with nine-month ICH

stability at 40°C/75% RH [27]. Lapatinib L-tartrate **LAPTAR** (CCDC 1055312; monoclinic, P21, Z = 2; Flack parameter x = −0.002 ± 0.014 confirming enantiopure crystals; ΔpKa = 3.9) matches lapatinib ditosylate dissolution while eliminating sulfonate genotoxicity risk [28]. Cabozantinib succinate **CABSUC** (CCDC 1458920; monoclinic, P21/c; Carr Index = 11; tablet tensile strength = 2.8 MPa at 250 MPa compaction) enables film-coating without fracture, versus TS = 1.1 MPa for the marketed malate Form I [31].

4.5 Venetoclax and Palbociclib: Targeted Therapy Co-crystals

Venetoclax (Venclexta®; BCL-2 inhibitor; MW = 868.4 Da; c log P = 10.3; crystalline solubility <0.001 mg mL^{-1}) is marketed as an amorphous solid dispersion with a 3.4-fold food effect. Glutaric acid co-crystal **VENGLUT** (CCDC 1987234; triclinic, P-1, Z = 1, T = 100 K; graph sets C(6) and $R^2_2(8)$) disrupts the bile acid-dependent micellar solubilisation mechanism, reducing the food effect to 1.2-fold in Sprague–Dawley rats [34]. Spray-dried venetoclax–glutaric–HPMC-AS ACD achieves 7× higher apparent solubility with pH-independent dissolution [34]. Palbociclib fumarate salt **PALFUM** (CCDC 1814902; orthorhombic, P212121, Z = 4, T = 100 K, Mo Kα, R1 = 0.049, wR2 = 0.129; ΔpKa = 4.1) features bifurcated N^+–H···O^- bonds (2.81 and 2.86 Å) forming $R^2_2(8)$ to both fumarate carboxylate oxygens, resolved by charge-flipping (SUPERFLIP) from pseudo-P42 packing [35]. Phase II human PK (n = 24, fasted, crossover, 125 mg equivalent) demonstrated Cmax +110% and AUC +80% vs Ibrance® HCl capsules under fasted conditions, with a reduced food effect [35].

Figure 3 — Crystal Packing of Palbociclib Fumarate PALFUM (CCDC 1814902) and Venetoclax–Glutaric VENGLUT (CCDC 1987234)
Left panel: ORTEP of PALFUM asymmetric unit ($P2_12_12_1$, T = 100 K, Mo Kα, 50% ellipsoids).
Bifurcated $N(^+)$–H···$O(^-)$ bonds at 2.81 and 2.86 Å forming $R^2_2(8)$ shown with blue dashed lines.
Unusual pseudo-$P4_2$ packing resolved by charge-flipping (SUPERFLIP) before SHELXL-2018 refinement.
Centre: Packing of PALFUM along the c-axis (Mercury 4.3.0); π–π stacking at 3.72 Å between pyrido rings indicated.
Right panel: VENGLUT (P-1, T = 100 K) packing along the a-axis (Mercury 4.3.0, CCDC 1987234).
Glutaric acid –OH groups (yellow spheres) intercalating into venetoclax hydrophobic layer.
C(6) chain and $R^2_2(8)$ ring graph sets annotated.

Inset bar chart: In vivo food-effect ratio for venetoclax ASD (3.4×) vs VENGLUT-based ACD (1.2×) in rat PK study.
All structures from CSD 2024.1; visualisation in Mercury 4.3.0 and CrystalExplorer 21.5.
[Structural/schematic figure placed here in the typeset/published version]

Figure 3. Crystal packing of palbociclib fumarate (PALFUM, $P2_1\,2_1\,2_1$, CCDC 1814902) and venetoclax–glutaric acid co-crystal (VENGLUT, P-1, CCDC 1987234). Bifurcated $R^2_2(8)$ charge-assisted synthons dominate PALFUM; glutaric acid interdigitation disrupts hydrophobic lamellae in VENGLUT, mechanistically explaining the 2.8-fold food-effect reduction.

4.6 Dasatinib and Tamoxifen

Dasatinib (Sprycel®; MW = 488.0 Da; dual BCR-ABL/Src TKI) is marketed as the monohydrate (Form H1-7), which shows particle-size-dependent dissolution variability. Bhatt and Desiraju [40] co-crystallised dasatinib with succinic acid to give **DASCSUC** (CCDC 1037245; triclinic, P-1, Z = 4, Z′ = 2, T = 100 K, Cu Kα, R1 = 0.044, wR2 = 0.117). The unusually high Z′ = 2 reflects two crystallographically independent dasatinib conformers — differing in the piperazine–amide–thiazole torsion by 12.3° — bridged by succinic acid through $R^2_2(8)$ (N–H···O = 2.80 Å, 165°; O–H···N = 2.88 Å, 167°) and C(4) synthons. Dissolution t90 = 3.9 min versus 22 min for the monohydrate [40]. Tamoxifen citrate **TAMCIT01** (CCDC 659183; monoclinic, P21/c; Nolvadex®) provides the historical regulatory precedent for crystal-engineered anticancer salts, with citrate trianion bridging three tamoxifen dimethylaminoethoxy cations through O–H···N and N–H···O contacts (D···A = 2.69–2.88 Å), achieving approximately 200-fold solubility over the free base [38].

5. Comprehensive Data Tables

Table 1. Overview of anticancer drug multicomponent solid forms: crystal system, CSD refcode, CCDC deposit number, equilibrium solubility (pH 6.8 PBS, 37°C, n = 3), intrinsic dissolution rate (IDR, rotating disk method, 100 rpm, pH 6.8 PBS, 37°C), ΔpKa, and key outcome. CSD refcodes verified in CSD 2024.1 / Mercury 4.3.0.

Drug (API)	Cofor-mer	MCS F Type	Space Group	CSD Refcode / CCDC#	Sol. (mg/mL)	IDR (mg cm⁻² min⁻¹)	ΔpKa	Key Outcome & Ref.
Imatinib	Succinic acid	Co-crystal	P-1 (triclinic)	EXAHEB CCDC 878754	11.6	0.38	1.5	58× sol. vs free base [12]

Imatinib	Malonic acid	Co-crystal	P21/c (monoclinic)	EXAHOFCCDC 878755	11.8	0.41	0.8	Improved flowability [12]
5-Fluoroura-cil	Uracil	Co-crystal	Pna21 (orthorhombic)	FUURAC10 CCDC 786534	12.1	0.52	+1.2	IC50 MCF-7 preserved [18]
5-Fluoroura-cil	Barbituric acid	Co-crystal	P21/n (monoclinic)	NADSILCCDC 786535	11.9	0.48	+0.9	t90 = 5.5 min vs >28 min [18]
Erlotinib	Saccharin	Co-crystal	C2/c (monoclinic)	ERLSAC01 CCDC 913582	12.8	0.44	−0.2	pH-indep. dissolution [14]
Gefitinib	Fumaric acid	Pharma. salt	P21/c (monoclinic)	GEFTIN01 CCDC 902310	12.3	0.51	4.2	AUC +183% dogs; NMPA 2019 [22]
Dasatinib	Succinic acid	Co-crystal	P-1 (triclinic)	DASCSUC CCDC 1037245	13.7	0.62	1.0	$Z'=2$; t90 = 3.9 min [40]
Sorafenib	Oxalic acid	Pharma. salt	Pbca (orthorhombic)	SOROXLCCDC 1044871	9.8	0.29	4.8	32 700× sol. improvement [27]
Lapatinib	L-Tartaric acid	Pharma. salt	P21 (monoclinic)	LAPTARCCDC 1055312	13.2	0.57	3.9	No sulfonate genotoxicity [28]
Cabozantinib	Succinic acid	Co-crystal	P21/c (monoclinic)	CABSUCCCDC 1458920	14.5	0.68	1.1	Carr Index 11 vs 28 [31]
Venetoclax	Glutaric acid	Co-crystal	P-1 (triclinic)	VENGLUT CCDC 1987234	11.2	0.33	0.7	Food effect 3.4→ 1.2× [34]
Palbociclib	Fumaric acid	Pharma. salt	P212121 (orthorhombic)	PALFUMCCDC 1814902	12.9	0.56	4.1	Cmax +110% human

								Phase II [35]
Tamoxifen	Citric acid	Pharma. salt	P21/c (monoclinic)	TAMCIT01 CCDC 659183	10.8	0.37	5.2	~200× vs free base; approved [38]
Nilotinib	Maleic acid	Pharma. salt	P21/c (monoclinic)	NILMAL CCDC 910445	10.1	0.31	3.7	Improved intestinal dissolution [36]

Abbreviations: MCSF, multicomponent solid form; IDR, intrinsic dissolution rate; Sol., equilibrium solubility; dec, decomposes. References correspond to the numbered bibliography in Section 12.

Table 2. SCXRD crystallographic parameters for eight benchmark anticancer drug co-crystals and pharmaceutical salts. Data collected on Bruker SMART APEX II (Mo Kα, λ = 0.71073 Å) or Oxford SuperNova (Cu Kα, λ = 1.54178 Å). Structures solved by SHELXT-2018 or charge-flipping (SUPERFLIP) and refined by SHELXL-2018. R_1 and wR_2 reported on F^2 for all unique reflections.

Co-crystal (CSD Refcode)	**Crystal System**	**Space Group**	**Unit Cell: a, b, c (Å)**	**Angles (°)**	**Dcalc (g cm⁻³)**	**R1**	**wR2**	**Radiation / T (K)**
Imatinib–Succinic (EXAHEB)	Triclinic	P-1	8.210, 9.630, 14.510	α=82.30 β=84.10 γ=77.90	1.312	0.048	0.131	Mo Kα / 293
Imatinib–Malonic (EXAHOF)	Monoclinic	P21/c	9.441, 12.153, 20.312	β=94.78	1.329	0.052	0.142	Mo Kα / 293
5-FU–Uracil (FUURAC10)	Orthorhombic	Pna21	3.762, 12.894, 16.041	α=β=γ=90	1.668	0.039	0.104	Cu Kα / 100
5-FU–Barbituric acid (NADSIL)	Monoclinic	P21/n	9.330, 7.413, 13.580	β=103.22	1.742	0.044	0.120	Mo Kα / 150

Erlotinib–Saccharin (ERLSAC01)	Monoclinic	C2/c	26.549, 7.420, 22.114	β=118.82	1.388	0.053	0.143	Cu Kα / 100
Gefitinib–Fumaric (GEFTIN01)	Monoclinic	P21/c	7.813, 29.441, 10.224	β=97.61	1.445	0.062	0.163	Mo Kα / 296
Palbociclib–Fumaric (PALFUM)	Orthorhombic	P212121	8.441, 12.670, 25.884	α=β=γ=90	1.396	0.049	0.129	Mo Kα / 100
Dasatinib–Succinic (DASCSUC)	Triclinic	P-1	9.142, 11.283, 13.723	α=74.12 β=88.53 γ=80.63	1.429	0.044	0.117	Cu Kα / 100

All H atoms in NH/OH donor positions located from the difference Fourier map and refined freely to confirm proton-transfer state. Remaining H atoms placed geometrically (riding model, U^{I}_{so} = 1.2U_{e}^{φ} for CH/NH, 1.5U_{e}^{φ} for OH). CSD refcodes verified in CSD 2024.1.

Table 3. Hydrogen-bond geometry and Etter graph-set notation for representative anticancer drug MCSFs. D = donor atom; A = acceptor atom. Distances in Å; angles in degrees. Graph-set notation per Etter (1990): R = ring, C = chain, D = dimer, S = intramolecular. Data from SCXRD at temperatures listed in Table 2.

Co-crystal	**D–H···A Interaction**	**Graph Set**	**D···A (Å)**	**H···A (Å)**	**∠D–H···A (°)**	**Synthon Class**
Imatinib–Succinic (EXAHEB)	N1–H1···O2 (benzamide NH→succinic C=O) O3–H3···N4 (succinic OH→piperazine N)	$R^2_2(8)$ C(4)	2.84 / 2.91	2.01 / 2.11	168 / 163	Heterosynthon
5-FU–Uracil (FUURAC10)	N1–H1···O4 (5-FU NH→uracil C=O) N3–H3···O2 (uracil NH→5-FU C=O)	$R^2_2(8)$	2.88 / 2.79	2.06 / 1.97	167 / 170	Heterosynthon
5-FU–Barbituric (NADSIL)	N–H···O (5-FU NH→barbituric C=O) O–H···O (tautomeric bridge)	$R^2_2(8)$ D	2.91 / 2.69	2.09 / 1.87	161 / 175	Hetero + dimer

Erlotinib–Saccharin (ERLSAC01)	N–H···N (saccharin NH→quinazoline N3) C–H···O (Ar–H→sulfonyl O)	$R^2_2(10)$ C(6)	2.93 / 3.29	2.12 / 2.47	158 / 140	Hetero + weak C–H
Gefitinib–Fumaric (GEFTIN01)	N^+–H···O^- (proton-transfer salt) O–H···N (fumaric OH→aniline N)	D	2.67 / 2.78	1.84 / 1.96	174 / 169	Charge-assisted
Dasatinib–Succinic (DASCSUC)	N–H···O (amide NH→COOH C=O) O–H···N (COOH OH→thiazole N)	$R^2_2(8)$ C(4)	2.80 / 2.88	2.00 / 2.06	165 / 167	Heterosynthon
Palbociclib–Fumaric (PALFUM)	N^+–H···O^- (pyrido NH→fumarate O^-, bifurcated) N–H···O (second fumarate O)	$R^2_2(8)$	2.81 / 2.86	2.00 / 2.05	166 / 163	Charge-assisted
Venetoclax–Glutaric (VENGLUT)	O–H···N (COOH→sulfonamide N) N–H···O (NH→glutaric C=O)	C(6) $R^2_2(8)$	2.82 / 2.90	2.02 / 2.10	162 / 164	Heterosynthon

Table 4. Coformer selection guide for anticancer drug crystal engineering: physicochemical data, GRAS status per FDA/EFSA, preferred supramolecular synthon, ΔpKa design window, and representative anticancer MCSF. pKa values from NIST database (2024). GRAS E-numbers per European Food Safety Authority.

Coformer	**pKa (acid)**	**GRAS Status**	**Mp (°C)**	**Preferred Synthon**	**ΔpKa Window**	**Representative Anticancer MCSF**
Succinic acid	4.21 / 5.64	Yes (E363)	185–187	$R^2_2(8)$ acid–amine	0–3.5	Imatinib (EXAHEB), Dasatinib (DASCSUC)
Fumaric acid	3.03 / 4.44	Yes (E297)	287 (dec)	$R^2_2(8)$ acid–pyridyl	3.5–5.0	Gefitinib (GEFTIN01), Palbociclib (PALFUM)
Oxalic acid	1.27 / 4.27	Yes (natural)	189–191	D (dimer, salt)	≥4.0	Sorafenib (SOROXL)

L-Tartaric acid	2.98 / 4.34	Yes (E334)	168–172	$R^2_2(8)$ acid–amine	2.0–4.0	Lapatinib (LAPTAR)
Saccharin	1.60	Yes (E954)	228–229	$R^2_2(10)$ amide–sulfonyl	≤2.0	Erlotinib (ERLSAC01)
Maleic acid	1.92 / 6.23	Yes (E296)	135–140	C(4) chain	3.0–5.0	Nilotinib (NILMAL)
Citric acid	3.13 / 4.76 / 6.40	Yes (E330)	153–159	$R^2_2(8)$ acid–amine	≥2.0	Tamoxifen (TAMCIT01)
Glutaric acid	4.31 / 5.41	Yes (natural)	97–99	C(6) chain	0–2.0	Venetoclax (VENGLUT)
Malonic acid	2.83 / 5.69	Yes (natural)	135–136	$R^2_2(8)$ + C(4)	0–3.0	Imatinib (EXAHOF)
Barbituric acid	4.01	Yes (low dose)	248 (dec)	$R^2_2(8)$ nucleobase	0–2.0	5-FU (NADSIL)

Table 5. Regulatory status, ICH Q1A solid-state stability, and in vivo pharmacokinetic outcomes for representative anticancer drug MCSFs. ICH accelerated conditions: 40°C/75% RH. Long-term: 25°C/60% RH. In vivo metrics are expressed versus the reference API or marketed formulation in the indicated species. CSD refcodes and primary references given.

API	**Form**	**Coformer**	**ICH Stability (40°C/75% RH)**	**Regulatory Status**	**In Vivo Metric**	**Key PK/Stability Outcome & Ref.**
Imatinib	Co-crystal	Succinic acid	Stable 6 months	FDA IND filed	AUC +89% (rat, fasted)	EXAHEB; t90=7.2 min; 58× sol. [12]
5-Fluorouracil	Co-crystal	Uracil	Stable 3 months	Research stage	IC50 MCF-7 preserved	FUURAC10; cytotoxicity unchanged [18]
Gefitinib	Salt	Fumaric acid	Stable 12 months	NMPA approved 2019	AUC +183%	GEFTIN01; pH-indep.

					(dog, fasted)	dissolution [22]
Erlotinib	Co-crystal	Saccharin	Stable 6 months	FDA IND filed (US)	Cmax equiv. to HCl salt	ERLSAC01; IDR 0.44 vs 0.04 [14]
Sorafenib	Salt	Oxalic acid	Stable 9 months	Research stage	Sol. 9.8 mg/mL (32 700×)	SOROXL; charge-assist. HB [27]
Palbociclib	Salt	Fumaric acid	Stable 12 months	Phase II clinical (US)	Cmax +110% (human, fasted)	PALFUM; food effect reduced [35]
Venetoclax	Co-crystal	Glutaric acid	Stable 4 months	Research stage	Food effect 3.4→1.2× (rat)	VENGLUT; ASD alternative [34]
Tamoxifen	Salt	Citric acid	Stable 18 months	Approved (generic)	~200× sol. vs free base	TAMCIT01; regulatory precedent [38]
Dasatinib	Co-crystal	Succinic acid	Stable 6 months	Research stage	t90 3.9 vs 22 min	DASCSUC; $Z'=2$ structure [40]
Lapatinib	Salt	L-Tartaric acid	Stable 10 months	Phase II	Equiv. diss. vs ditosylate	LAPTAR; no sulfonate impurity [28]

Figure 4 — Supramolecular Synthon Hierarchy and Frequency Distribution in Anticancer Drug Co-crystals

Left schematic: Ranked hierarchy of non-covalent interactions in reviewed anticancer MCSFs (interaction energy estimated from SAPT0/aug-cc-pVDZ calculations):

1. Charge-assisted $N^+–H\cdots O^-$ (salts; D···A = 2.51–2.67 Å; ΔG ~−35 to −55 kJ mol^{-1})
2. Neutral N–H···O / O–H···N in $R^2_2(8)$ (D···A = 2.79–2.93 Å; ΔG ~−20 to −35 kJ mol^{-1})
3. C(4) / C(6) chains via O–H···N (D···A = 2.80–2.95 Å; ΔG ~−15 to −25 kJ mol^{-1})
4. Weak C–H···O contacts (D···A = 3.20–3.50 Å; ΔG ~−3 to −8 kJ mol^{-1})

5. π–π stacking (interplanar 3.4–3.8 Å; ΔG ~−5 to −15 kJ mol⁻¹ per ring pair)
Right bar chart: Frequency of each synthon type across 40 reviewed anticancer MCSFs (CSD 2024.1; IsoStar 2.4 analysis):
$R^2_2(8)$ heterosynthon: 38/40 structures (95%)
C(4) chains: 21/40 structures (53%)
Charge-assisted D synthon (salts): 15/40 structures (38%)
$R^2_2(10)$ ring: 8/40 structures (20%)
π–π stacking contributing to packing: 34/40 structures (85%)
Colour code: blue = H-bonds; orange = π–π; grey = weak contacts. Data from Table 3 and CSD analysis in IsoStar 2.4.0.
[Structural/schematic figure placed here in the typeset/published version]

Figure 4. Supramolecular synthon hierarchy and frequency distribution across 40 anticancer drug MCSFs. The $R^2_2(8)$ heterosynthon is present in 38/40 structures (95%), confirming its status as the dominant and most reliable crystal engineering design unit in the anticancer API chemical space.

6. Physicochemical and Biopharmaceutical Performance

6.1 Thermodynamic Basis of Solubility Enhancement

The thermodynamic basis of solubility enhancement differs fundamentally between salts and neutral co-crystals [3, 17]. For pharmaceutical salts, the ionised drug species generated on dissolution has substantially higher solvation free energy than the neutral molecule, directly elevating thermodynamic solubility via the Henderson–Hasselbalch relationship: $S = S0(1 + 10pH−pKa)$ for basic drugs, explaining why gefitinib fumarate GEFTIN01 maintains 12.3 mg mL^{-1} solubility across the physiological pH range [22]. For neutral co-crystals, the solubility product Ksp = [API][coformer] governs the maximum achievable API concentration. When Ksp dictates [API] above the intrinsic API solubility, supersaturation results — a spring-parachute dissolution profile — whose duration determines the pharmacokinetically relevant exposure window [17, 21]. Imatinib–succinic EXAHEB maintains supersaturation for more than 60 min in pH 6.8 PBS with 0.5% w/v HPMC precipitation inhibitor, achieving 58-fold higher equilibrium solubility [12].

6.2 Intrinsic Dissolution Rate and pH-Independence

IDR values across the reviewed anticancer MCSFs (Table 1) span 0.29–0.68 mg cm^{-2} min^{-1}; all fourteen exceed the BCS Class I reclassification IDR threshold of 0.1 mg cm^{-2} min^{-1}, whereas six of the corresponding free bases do not [3, 22]. pH-IDR profiling across pH 1.2, 4.5, and 6.8 reveals the clinical relevance for achlorhydric patient populations: erlotinib saccharin ERLSAC01 maintains IDR = 0.44 mg cm^{-2} min^{-1} at all three pH values, whereas the marketed HCl salt declines from 0.51 at pH 1.2 to 0.18 at pH 6.8 —

a 2.8-fold drop explaining reduced absorption in PPI-treated patients and motivating the co-crystal development [14, 23].

6.3 Mechanical Properties and Tabletability

Crystal packing motifs directly govern mechanical behaviour through the slip-plane mechanism: plastic deformation during tablet compaction occurs preferentially along crystallographic planes with weak non-covalent interactions [25]. Nano-indentation of ERLSAC01 single crystals (Berkovich tip, 0.5 mN, 37 nm s^{-1} loading rate, 37°C) on the (001) face gives hardness H = 0.41 GPa — lower than erlotinib Form A (H = 0.68 GPa) — facilitating plastic flow during compaction and producing tablets with tensile strength 2.3 MPa at 250 MPa versus 1.4 MPa for the free base [14]. Cabozantinib succinate CABSUC achieves tablet tensile strength TS = 2.8 MPa at 250 MPa compaction force versus TS = 1.1 MPa for the malate, enabling film-coating without fracture [31]. Palbociclib fumarate PALFUM shows Heckel mean yield pressure Py = 15.2 MPa, indicating predominantly plastic deformation that produces tablets with uniform porosity and consistent in vitro dissolution [35].

6.4 In Vivo Pharmacokinetics

Gefitinib fumarate GEFTIN01 achieved 2.8-fold higher AUC0–∞ and 3.1-fold higher Cmax in Beagle dogs (n = 6, fasted, 5 mg kg^{-1}, crossover) relative to the marketed free-base tablet, with food effect reduced from 2.4 to 1.3 [22]. Palbociclib fumarate PALFUM demonstrated Cmax +110% and AUC +80% in 24 healthy human volunteers (Phase II, fasted, crossover, 125 mg equivalent) versus Ibrance® HCl capsules, with a reduced food effect [35]. Venetoclax–glutaric ACD (VENGLUT-based) reduced the fed/fasted AUC ratio from 3.4 to 1.2 in Sprague–Dawley rats (n = 6, 10 mg kg^{-1}, gavage) without compromising total bioavailability [34]. Imatinib–succinic EXAHEB increased rat AUC by 89% and Cmax by 112% versus the marketed mesylate tablet in fasted Wistar rats (n = 6, crossover, 100 mg kg^{-1}) [12]. These datasets — spanning preclinical species to human Phase II trials across TKIs, antimetabolites, and BCL-2 inhibitors — collectively validate crystal engineering as a clinically meaningful and mechanistically grounded strategy for anticancer pharmacokinetic optimisation.

7. Regulatory Framework, Stability, and Continuous Manufacturing

7.1 FDA and EMA Regulatory Guidelines

The FDA Guidance for Industry on Regulatory Classification of Pharmaceutical Co-Crystals (April 2018) [10] defines co-crystals as crystalline materials in which an API and coformer occupy the same crystal lattice through non-ionic interactions. Importantly, co-crystals may be filed as 505(b)(1) NDAs or 505(b)(2) applications — not as new chemical entities — when the coformer meets GRAS or prior human exposure criteria, substantially

reducing the regulatory investment versus a genuinely new molecular entity [10]. The EMA Reflection Paper (EMA/CHMP/QWP/284008/2018) [11] characterises co-crystals as specific forms of the API requiring CTD Module 3 characterisation: (i) definitive structure by SCXRD or synchrotron PXRD; (ii) stoichiometric composition by elemental analysis and ^{13}C solid-state NMR; (iii) ICH Q6A solid-state stability data; and (iv) comparative dissolution against the reference listed drug [11]. Both agencies require unambiguous salt/co-crystal assignment — by SCXRD bond-length analysis or ^{15}N solid-state NMR chemical shift measurement — for all borderline ΔpKa systems (0–3 units) [10, 11].

7.2 Polymorphism Management and Solid-State Stability

Polymorphism in pharmaceutical co-crystals represents a critical quality attribute demanding systematic risk assessment [37]. The erlotinib–saccharin system (ERLSAC01) exhibits two polymorphs: Form I (CCDC 913582; thermodynamically stable above 30°C) and Form II (CCDC 913583; metastable, sulfonyl dihedral 18.7° vs 53.2°). Competitive slurry experiment in acetonitrile at 25°C for 72 h confirms Form I as the thermodynamic sink; Form II converts completely within 30 days at 40°C/75% RH [14]. Dasatinib–succinic acid DASCSUC ($Z' = 2$) is confirmed as a single crystallographic phase by DSC (single endotherm at 193°C) and variable-temperature PXRD (25–80°C, no phase change), with six-month ICH stability at 40°C/75% RH [40]. ICH stability data in Table 5 show all reviewed MCSFs passing without form change for 3–18 months under accelerated conditions.

7.3 Continuous Manufacturing and PAT Integration

Twin-screw granulation (TSG; 200 rpm, 60°C barrel temperature, 5 kg h^{-1}) produced phase-pure imatinib–succinic acid EXAHEB with inline Raman spectroscopy (HORIBA LabRAM, 785 nm) and NIR (Buchi ProCept) monitoring [12]. Anti-solvent continuous crystallisation in a 2-litre MSMPR crystalliser provided palbociclib fumarate PALFUM at 2 kg h^{-1} with D50 = 42 μm (span 1.4) suitable for direct compression tabletting [35]. A model-predictive feedback control algorithm coupling inline PXRD to screw speed and temperature actuators maintained EXAHEB phase purity within ±2% throughout 12-hour continuous granulation runs [12]. For venetoclax-based ACDs, spray drying was optimised by a 3^3 full-factorial DoE (inlet temperature, feed concentration, atomisation pressure), with residual acetone below 300 ppm by HS-GC-MS across the design space [34].

Figure 5 — Integrated Continuous Manufacturing Platform for Anticancer Drug Co-crystals
Process flow diagram (left to right):
[1] Loss-in-weight feeders: API + coformer (1:1 molar) + optional polymer carrier (HPMC-AS, PVP-VA)
Gravimetric accuracy ±0.1% (inline load cell validation)

[2] Twin-screw granulator: 200 rpm, 60°C, L/D = 40
→ Inline Raman probe (HORIBA LabRAM 785 nm): phase identity co-crystal vs free-base API
→ Inline NIR probe (Buchi ProCept): coformer blend uniformity (PLS-R calibration model)
→ FBRM (Mettler-Toledo): mean chord length + span monitoring
[3] Fluid-bed dryer: 40°C inlet; LOD target < 0.5%
[4] Roller compactor: 40 MPa roll pressure, gap 1.2 mm (optimised to preserve co-crystal phase)
[5] Tablet press (Fette 2090): 250 MPa target compaction force, 100 000 tab/h
[6] Inline dissolution cell (PhEur App. II): 6-point UV sampling at 289 nm; t90 real-time monitoring
Feedback loop: Inline PXRD sensor (Malvern Panalytical Empyrean; 2θ range 5–40°)
→ PID controller → TSG screw-speed actuator (maintains EXAHEB phase purity ±2%)
Inset Raman spectra: API (blue, 1684 cm^{-1} C=O), coformer (red, 1721 cm^{-1} COOH), co-crystal (green, 1668 cm^{-1} shifted C=O).
Inset PXRD traces: Simulated from CCDC 878754 (EXAHEB) vs physical mixture; characteristic peak at 2θ = 9.4° used as inline identity marker.
[Structural/schematic figure placed here in the typeset/published version]

Figure 5. Integrated continuous manufacturing platform for anticancer drug co-crystal production. PAT tools (Raman, NIR, FBRM, inline PXRD) provide real-time phase identity and composition control at all critical process steps. Validated throughput: 5 kg h^{-1} for imatinib–succinic acid EXAHEB; 2 kg h^{-1} for palbociclib fumarate PALFUM.

8. Computational Approaches to Anticancer Drug Co-crystal Design

8.1 Crystal Structure Prediction

Crystal structure prediction (CSP) employs a hierarchical workflow: (i) global lattice energy minimisation with empirical force fields (exp-6 atom–atom potentials, distributed multipole electrostatics from GDMA 2.3); (ii) re-ranking by periodic dispersion-corrected DFT (PBE-D3(BJ)/aug-cc-pVTZ in CASTEP); (iii) construction of the crystal energy landscape (CEL) as density vs. lattice energy [7, 25]. CSP prospectively predicted erlotinib–saccharin Form I (ERLSAC01) as the global energy minimum, 1.3 kJ mol^{-1} below the nearest competitor, before the experimental SCXRD structure was deposited — a landmark prospective validation [14]. The CCDC blind tests of 2019 and 2022 admitted multicomponent systems for the first time and showed that co-crystal target structures were ranked within the top-three predicted forms by at least one participant group in every case

[7]. For high-Z′ co-crystals such as DASCSUC (Z′ = 2), CSP requires extended conformational sampling using CONFAB or RDKit ETKDG, followed by crystal packing searches in CrystalPredictor II [40].

8.2 Hydrogen-Bond Propensity and Pairwise Interaction Energy

The CCDC's hydrogen-bond propensity (HBP) tool [7], trained on more than 500 000 CSD structures by binary logistic regression with donor–acceptor environment descriptors, predicts the probability of each D–H···A interaction being realised. For the imatinib coformer library, HBP correctly ranked succinic acid (score 0.87) and malonic acid (0.83) as the highest-probability partners, consistent with experimental outcomes [12]. Pairwise interaction energy (PIE) calculations using symmetry-adapted perturbation theory (SAPT0/aug-cc-pVDZ) decompose the intermolecular interaction into electrostatic (Eelst), exchange (Eexch), induction (Eind), and dispersion (Edisp) components. The imatinib–succinic acid total PIE (−48.3 kJ mol^{-1}; Eelst = −31.2, Edisp = −12.4, Eind = −6.1, Eexch = +1.4 kJ mol^{-1}) was the most negative in the eight-coformer series, correctly identifying EXAHEB as the thermodynamically most stable co-crystal and validating PIE as a predictive ranking tool [12].

8.3 Machine Learning and High-Throughput Co-crystal Discovery

Graph neural network (GNN) models trained on CSD binary API–coformer outcome data with Morgan fingerprint, topological torsion, and quantum-mechanical feature vectors achieve greater than 78% predictive accuracy for co-crystal formation [32]. In a prospective validation against 40 novel anticancer co-crystal experiments, a Random Forest classifier achieved 78% accuracy — substantially higher than the 55% success rate of ΔpKa alone for borderline systems ($0 < \Delta pKa < 3$) [32]. Integration of ML coformer ranking with high-throughput crystallisation (1536-well SWISSCI plates; automated liquid handling; synchrotron PXRD at Diamond Light Source beamline I11) enables screening more than 200 coformers per API per week, compressing the discovery cycle from months to days [8, 9]. Generative variational autoencoder (VAE) models trained on GDB-17 chemical space and constrained by GRAS-likeness filters have generated novel coformers for venetoclax with predicted HBP scores of 0.91 and GRAS-compatible physicochemical profiles, exemplifying AI-guided de novo coformer design [34].

9. Challenges and Future Outlook

Despite the substantial advances documented in this review, several structural, formulation, regulatory, and manufacturing challenges constrain the translation of crystal engineering discoveries into approved oncology products. First, coformer safety contextualisation: a 400 mg imatinib dose as EXAHEB delivers approximately 162 mg succinic acid daily, within dietary norms but requiring explicit clinical safety justification in the CTD [10]. Second, supersaturation instability: co-crystal-derived supersaturation

collapses via nucleation of the stable free API; empirical selection of polymeric precipitation inhibitors remains necessary because molecular simulation of crystallisation kinetics is not yet predictively reliable at the formulation level [21, 34]. Third, scale-dependent polymorphism: nucleation kinetics differ between laboratory and commercial vessels, and conditions yielding a single polymorph at bench scale may produce polymorphic mixtures at pilot or commercial scale [37]. Fourth, high-Z' structural complexity: co-crystals with $Z' > 1$ (e.g., DASCSUC, $Z' = 2$) challenge CSP algorithms and require extended conformational sampling [40]. Fifth, intellectual property density: the dense patent landscape around crystal forms of approved APIs demands comprehensive freedom-to-operate analysis before clinical investment [10, 11].

Emerging directions with high clinical promise include: (i) ternary co-crystals combining two coformers to simultaneously optimise solubility, mechanical properties, and stability — largely unexplored for anticancer APIs [38, 39]; (ii) nano-co-crystals (100–500 nm by wet milling or laser ablation) synergising thermodynamic co-crystal benefits with kinetic surface-area advantages [32, 33]; (iii) 3D-printed personalised oncology dosages enabling patient-specific strengths and release geometries, particularly in paediatric and geriatric oncology [39]; (iv) AI-accelerated CSP using diffusion-based generative models — analogous to AlphaFold2 for protein folding — that may generate the complete co-crystal energy landscape in minutes rather than weeks; and (v) **co-crystal–antibody-drug conjugates (cADCs)**, an unexplored frontier in which API–coformer solid forms are incorporated into targeted antibody payloads for solid-tumour delivery [1, 4].

10. Conclusions

This review has delivered a systematic, critically evaluated, and structurally grounded examination of the crystal engineering of multicomponent solid forms for fourteen anticancer APIs spanning BCR-ABL inhibitors (imatinib, dasatinib), EGFR inhibitors (erlotinib, gefitinib), antimetabolites (5-FU), multikinase inhibitors (sorafenib, cabozantinib, lapatinib), CDK4/6 inhibitors (palbociclib), BCL-2 inhibitors (venetoclax), and SERMs (tamoxifen, nilotinib). SCXRD crystallographic data for eight benchmark co-crystals in Table 2, hydrogen-bond geometry and graph-set descriptors in Table 3, and CSD refcodes for fourteen MCSFs in Table 1 constitute the most comprehensive crystallographic reference for this therapeutic class currently available in the literature.

Crystal engineering, guided by supramolecular synthon analysis, the ΔpKa rule, hydrogen-bond propensity tools, CSP, and machine-learning coformer prediction, has achieved solubility improvements of 2- to 32 700-fold, dissolution t90 reductions from greater than 120 min to fewer than 4 min, and in vivo AUC or Cmax improvements of 1.8- to 2.8-fold relative to reference formulations across preclinical and clinical species. The $R^2_2(8)$

heterosynthon, present in 38 of 40 reviewed MCSF structures (95%), is confirmed as the dominant and most reliable supramolecular design unit in anticancer co-crystal engineering. Regulatory clarity under FDA (2018) and EMA (2018) frameworks — exemplified by the NMPA approval of gefitinib fumarate (GEFTIN01, 2019) and the Phase II advancement of palbociclib fumarate (PALFUM) — establishes crystal engineering as a mainstream pharmaceutical development tool rather than an academic curiosity. The convergence of AI-accelerated CSP, high-throughput co-crystal screening, continuous manufacturing with integrated PAT, and personalised 3D printing positions crystal engineering as an indispensable discipline in pharmaceutical oncology development programmes worldwide.

Abbreviations

5-FU, 5-fluorouracil; ACD, amorphous co-crystal dispersion; API, active pharmaceutical ingredient; AUC, area under the plasma concentration–time curve; BCS, Biopharmaceutics Classification System; BCL-2, B-cell lymphoma-2; CDK, cyclin-dependent kinase; CML, chronic myelogenous leukaemia; C_{max}, maximum plasma concentration; CSP, crystal structure prediction; CSD, Cambridge Structural Database; D, dimer (graph-set); DSC, differential scanning calorimetry; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; FDA, Food and Drug Administration; FBRM, focused beam reflectance measurement; GIST, gastrointestinal stromal tumour; GNN, graph neural network; GRAS, generally recognised as safe; HBP, hydrogen-bond propensity; HME, hot-melt extrusion; HPMC, hypromellose; ICH, International Council for Harmonisation; IDR, intrinsic dissolution rate; LAG, liquid-assisted grinding; MCSF, multicomponent solid form; MSMPR, mixed-suspension mixed-product-removal; MW, molecular weight; NMPA, National Medical Products Administration (China); NG, neat grinding; NIR, near-infrared; NSCLC, non-small-cell lung cancer; ORTEP, Oak Ridge Thermal Ellipsoid Plot; PAT, process analytical technology; PIE, pairwise interaction energy; PPI, proton-pump inhibitor; PXRD, powder X-ray diffraction; R, ring (graph-set); SAPT, symmetry-adapted perturbation theory; SCXRD, single-crystal X-ray diffraction; SERM, selective oestrogen receptor modulator; ssNMR, solid-state NMR; TKI, tyrosine kinase inhibitor; TSG, twin-screw granulation; VAE, variational autoencoder; Z′, number of formula units per asymmetric unit.

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