CRYSTAL ENGINEERING OF PHARMACEUTICAL COCRYSTALS OF ANTIHYPERTENSIVE DRUGS: DESIGN STRATEGIES, STRUCTURAL ANALYSIS, AND BIOPHARMACEUTICAL OUTCOMES

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Abstract

Hypertension remains the leading modifiable risk factor for cardiovascular mortality, affecting more than 1.28 billion adults worldwide. The pharmacological management of hypertension relies on several classes of active pharmaceutical ingredients (APIs) — including angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, and beta-blockers — many of which suffer from intrinsically poor aqueous solubility, sub-optimal oral bioavailability, and physicochemical instability. Crystal engineering through pharmaceutical Cocrystallization has emerged as a potent, non-covalent solid-state strategy to address these challenges without structural modification of the parent drug molecule. This review provides a comprehensive and critical analysis of cocrystals of antihypertensive drugs prepared by crystal engineering methods, including solution crystallization, mechanochemical grinding, liquid-assisted grinding (LAG), slurry conversion, hot melt extrusion (HME), and spray drying. We survey the landscape of reported cocrystal systems covering all major antihypertensive drug classes — telmisartan, losartan, valsartan, irbesartan, candesartan, Olmesartan, amlodipine, hydrochlorothiazide, atenolol, metoprolol, carvedilol, nebivolol, and the landmark drug–drug cocrystal Entresto (sacubitril–valsartan, CSD: NAQLAU). Single-crystal X-ray diffraction (SCXRD) data, Cambridge Structural Database (CSD) refcodes, space group symmetry, unit cell parameters, and dominant supramolecular synthons are tabulated and discussed for each system. The mechanistic role of hydrogen bonding heterosynthon — including O–H···N, N–H···O, and tetrazole–amide motifs — in determining cocrystal stability, solubility, and dissolution behavior is examined in depth. Regulatory considerations from the US FDA, EMA, ICH, and PMDA are also addressed. This review serves as a consolidated reference for researchers pursuing crystal-engineering-based drug development for cardiovascular therapeutics.

Keywords: *pharmaceutical cocrystals; crystal engineering; antihypertensive drugs; supramolecular synthons; SCXRD; CSD; solubility enhancement; telmisartan; valsartan; hydrochlorothiazide; Entresto; mechanochemistry*

1. Introduction

Hypertension, defined as a sustained systolic blood pressure ≥130 mmHg or diastolic pressure ≥80 mmHg, constitutes the most prevalent non-communicable disease globally and a primary determinant of ischaemic heart disease, haemorrhagic stroke, renal failure, and heart failure.1 The World Health Organization estimates that approximately 1.28 billion adults aged 30–79 years are affected by hypertension globally, with fewer than half adequately controlled.2 Antihypertensive pharmacotherapy has evolved substantially over the past five decades, giving rise to a diverse therapeutic armamentarium that includes ARBs, ACE inhibitors, CCBs (dihydropyridine and non-dihydropyridine), thiazide and thiazide-like diuretics, and adrenergic receptor antagonists (α- and β-blockers).3

A major challenge that persists across these drug classes is poor physicochemical performance in the solid state, particularly inadequate aqueous solubility. The majority of ARBs (losartan, valsartan, telmisartan, irbesartan, candesartan, olmesartan) and several CCBs (amlodipine) and β-blockers (carvedilol, nebivolol) are classified under BCS Class II (high permeability/low solubility) or Class IV (low solubility/low permeability), as shown in Table 1. This creates formidable barriers to consistent oral bioavailability and poses significant challenges for the pharmaceutical scientist during drug product development.4,5

Crystal engineering — the rational design of functional molecular crystals through the deliberate exploitation of intermolecular interactions — offers an elegant route to address these physicochemical limitations.6 Pharmaceutical cocrystals, defined as crystalline solids composed of two or more neutral molecular components in a stoichiometric ratio held together by non-covalent interactions (primarily hydrogen bonds, but also π–π stacking, halogen bonds, and van der Waals interactions), represent one of the most versatile and regulatory-acceptable strategies for modifying the solid-state properties of APIs without altering their covalent chemical structure or pharmacological activity.7,8

The conceptual foundations of crystal engineering date to the seminal contributions of Schmidt (1971) on topochemical reactions.9 Desiraju's articulation of the crystal engineering concept in 1989 and the subsequent formalisation of the supramolecular synthon concept in 1995 — describing recurring, robust patterns of intermolecular interactions that can be reliably used to construct designed architectures — provided the intellectual framework for modern pharmaceutical cocrystal design.10,11 Etter's rules of hydrogen bonding (1990) and the development of the CSD by Allen and co-workers at the Cambridge Crystallographic Data

Centre provided powerful experimental and informatic tools to survey, classify, and exploit synthonic patterns across thousands of crystal structures.12,13

From a regulatory perspective, the US FDA issued guidance classifying pharmaceutical cocrystals as drug product intermediates (when the coformer is pharmacologically inactive) or as drug substances (when the coformer is itself pharmacologically active, as in drug–drug cocrystals, DDCs).14 The EMA's 2015 Reflection Paper similarly acknowledged cocrystals as a distinct solid-state form warranting systematic evaluation.15 These developments catalysed a wave of academic and industrial research into antihypertensive cocrystals, culminating in the 2015 FDA approval of Entresto — the iconic DDC of sacubitril and valsartan (CSD refcode: NAQLAU) — as the world's first marketed, large-scale pharmaceutical drug–drug cocrystal.16

This review aims to provide the most comprehensive and critically analysed survey of pharmaceutical cocrystals of antihypertensive drugs prepared by crystal engineering approaches. We systematically cover: (i) the molecular basis and design strategies for antihypertensive cocrystals; (ii) crystal engineering preparation methods and their comparative merits; (iii) SCXRD structural data, CSD refcodes, space group symmetry, unit cell parameters, packing motifs, and dominant supramolecular synthons; (iv) physicochemical property modulation including solubility, dissolution, bioavailability, and stability; (v) drug–drug cocrystals and their emerging role in combination hypertensive therapy; and (vi) regulatory and scale-up considerations for clinical translation.

Table 1. BCS classification, key physicochemical properties, and molecular weights of principal antihypertensive drugs amenable to cocrystal engineering. BCS = Biopharmaceutics Classification System; CCB = calcium channel blocker; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor–neprilysin inhibitor; DDC = drug–drug cocrystal.

Drug	Class	BCS	Solubility (mg/mL)	MW (g/mol)	log P
Amlodipine	CCB (DHP)	II	0.009	408.9	3.0
Losartan	ARB	II	~0.04	422.9	4.0
Valsartan	ARB	II	0.16	435.5	2.3
Telmisartan	ARB	II	<0.001	514.6	7.2
Irbesartan	ARB	II	<0.001	428.5	3.7
Candesartan	ARB	II/IV	~0.016	440.5	5.5
Olmesartan	ARB	II/IV	~0.008	558.6	4.0
Hydrochlorothiazide	Diuretic	IV	0.70	297.7	−0.07

Atenolol	β-blocker	III	13.3	266.3	0.16
Metoprolol	β-blocker	I	16.9	267.4	1.88
Carvedilol	α/β-blocker	II	0.583	406.5	3.16
Nebivolol	β-blocker	II	<0.010	405.4	3.86
Sacubitril/Valsartan	ARNi (DDC)	—	Improved	5748 (complex)	—

2. Fundamentals of Crystal Engineering and Pharmaceutical Cocrystals

2.1 Definition and Distinction from Salts, Solvates, and Polymorphs

A pharmaceutical cocrystal is a multi-component crystalline solid in which at least one component is an API and at least one other is a cocrystal former (coformer), bonded via non-covalent interactions in a defined stoichiometric ratio.17 Unlike salts — which require proton transfer between acidic and basic components and are therefore restricted to ionisable molecules — cocrystals can, in principle, be designed for any API regardless of its ionisation behaviour.18 This is of particular relevance for neutral ARBs such as telmisartan and candesartan, where salt formation is not straightforward.

The critical distinction between cocrystals and salts rests on the location of the transferred proton. SCXRD provides definitive evidence: when the proton is found on the coformer ($\Delta pKa \geq 3$), a salt is formed; when the proton remains on the API or is disordered, a cocrystal (or borderline case) exists.19 In solvates and hydrates, the additional lattice component is a solvent molecule (water or organic solvent), whereas coformers in pharmaceutical cocrystals are solid at room temperature and pharmaceutically acceptable.20 Polymorphs of a given API share the same chemical composition but differ in crystal packing; cocrystals introduce a chemically distinct second component.

2.2 Supramolecular Synthons as Design Tools

Etter's hydrogen bonding rules — (1) all good proton donors and acceptors are used in hydrogen bonding; (2) six-membered intramolecular H-bonds form first; (3) the best remaining donors and acceptors form intermolecular H-bonds — provide a practical framework for predicting likely cocrystal formation.21 Desiraju's supramolecular synthon concept further formalised recurring, structurally persistent patterns of H-bond interactions that can be identified from CSD surveys and deployed predictively in crystal engineering.10

For antihypertensive APIs, the most important synthons are: (a) the carboxylic acid–pyridine O–H···N heterosynthon, exploited in telmisartan cocrystals with pyridine-based

coformers; (b) the sulfonamide N–H···N and N–H···O synthons characteristic of hydrochlorothiazide cocrystals; (c) the tetrazole–amide N–H···N heterosynthon found in losartan cocrystals; and (d) the amide–amide N–H···O=C homosynthon that can compete with API–coformer heterosynthons and must be carefully managed during coformer selection.22,23 The Cambridge Structural Database, containing over 1.2 million crystal structures as of 2024, is the primary resource for identifying and validating synthon frequency and robustness.13

2.3 Coformer Selection Strategies

Rational coformer selection is the cornerstone of efficient cocrystal design. Several complementary approaches are employed: (i) pKa-based analysis, used to identify the optimal acid–base balance for maintaining neutral cocrystal character; (ii) molecular electrostatic surface potential (MESP) mapping, which visualises the complementary electrostatic surface features of the API and potential coformers and predicts the likelihood of heterosynthon formation; (iii) CSD survey-based supramolecular synthon analysis, identifying robust and frequent interaction patterns; (iv) Hansen solubility parameter (HSP) analysis for predicting solubility in common solvents and guiding solution-crystallisation conditions; and (v) emerging in silico computational methods including crystal structure prediction (CSP), molecular docking, and artificial intelligence-based screening.28

The choice of coformer is governed not only by its ability to form robust heterosynthons with the API, but also by pharmaceutical acceptability. The FDA GRAS (Generally Recognised As Safe) list of food additives and excipients, comprising over 3,000 substances, and the list of approved pharmaceutical excipients and drug substances, provide the primary pool from which coformers are drawn.8 Common coformers used in antihypertensive cocrystals include organic acids (saccharin, glutaric acid, succinic acid, maleic acid, oxalic acid, fumaric acid, citric acid), amides and nitrogen heterocycles (nicotinamide, isonicotinamide, picolinamide, pyrazinamide), and pharmaceutically active molecules (in DDCs).

3. Crystal Engineering Methods for Antihypertensive Cocrystals

A variety of crystal engineering methods have been employed for the preparation of antihypertensive pharmaceutical cocrystals, ranging from classical solution-based techniques to modern solvent-free mechanochemical and continuous manufacturing approaches. The selection of method impacts not only cocrystal yield and phase purity, but also particle size, crystal morphology, and SCXRD crystal quality. Table 2 summarises the principal methods with their relative advantages and limitations.

Table 2. Comparative overview of crystal engineering methods used in the preparation of antihypertensive pharmaceutical cocrystals. LAG = liquid-assisted grinding; HME = hot melt extrusion; SCF = supercritical fluid.

Method	Scale	Solvent Use	Advantages	Limitations
Slow Solvent Evaporation	Lab	High	SCXRD-quality crystals	Time-consuming, solvent waste
Mechanochemical Grinding	Lab–Pilot	None/minimal	Green, rapid, scalable	Limited crystal quality
Liquid-Assisted Grinding (LAG)	Lab–Pilot	Catalytic	Higher yield, better polymorph control	Stoichiometry sensitive
Slurry Conversion	Lab	Moderate	Thermodynamically stable products	Longer processing time
Hot Melt Extrusion (HME)	Pilot–Industrial	None	Continuous manufacturing, scalable	Thermal degradation risk
Spray Drying	Pilot–Industrial	Moderate	Nano-cocrystals, fast	Amorphous impurities
Supercritical Fluid (SCF)	Lab–Pilot	CO_2	Green, particle size control	High equipment cost

3.1 Solution Crystallisation

Slow solvent evaporation from a co-dissolved solution of API and coformer in a suitable organic solvent (ethanol, methanol, acetonitrile, ethyl acetate, or their mixtures) remains the gold-standard method for obtaining single crystals of diffraction quality suitable for SCXRD structure determination.29 In the synthesis of telmisartan–saccharin (TEL–SAC) and telmisartan–glutaric acid cocrystals reported by Sanphui and co-workers, slow evaporation from ethanol solutions yielded colourless block-shaped single crystals of dimensions typically 0.2–0.5 mm, permitting full SCXRD structure solution in the monoclinic P21/c and triclinic $P\bar{1}$ space groups, respectively.30 The solvent system critically influences the thermodynamic stability of the product polymorph; for valsartan cocrystals, methanol/water mixtures favour different crystal forms compared to pure ethanol.40

3.2 Mechanochemical Grinding

Neat grinding and LAG using a ball mill or mortar-and-pestle are among the most widely adopted green synthesis routes for pharmaceutical cocrystals. In LAG, a catalytic quantity of liquid (typically water, ethanol, or a few drops of solvent, $\eta = 0.25–1.0$ μL mg−1) is added to the physical mixture prior to grinding; the liquid accelerates molecular diffusion and nucleation kinetics without acting as a bulk solvent.31,32 Telmisartan–atenolol, irbesartan–atenolol, and hydrochlorothiazide–atenolol multicomponent solid forms were all prepared mechanochemically, with PXRD and DSC confirming their distinct solid-state identities.7 For HCT cocrystals with nicotinamide (NCT), piperazine (PPZ), and picolinamide (PCM), LAG in a planetary ball mill (500 rpm, 30 min) afforded phase-pure products characterised by SCXRD, PXRD, FTIR, and DSC.44

3.3 Slurry Conversion

In slurry conversion, a physical mixture of API and coformer is suspended in a minimal volume of solvent and stirred for extended periods (24–72 h) at controlled temperature. The method preferentially yields the thermodynamically most stable cocrystal form by allowing dissolution and re-crystallisation of metastable phases.29 Carvedilol–hydrochlorothiazide (CAR–HCT) cocrystals at a 2:0.5 molar ratio were prepared using this approach by Rao and co-workers using ethanol as the slurrying solvent, yielding phase-pure cocrystals confirmed by PXRD, DSC, and FTIR with a new onset melting temperature of 126.31°C — intermediate between pure carvedilol (117.12°C) and hydrochlorothiazide (276.03°C).9

3.4 Hot Melt Extrusion

HME enables the continuous, solvent-free production of pharmaceutical cocrystals by passing a molten physical mixture of API and coformer through a heated extruder barrel at temperatures above the eutectic melting point.32 Twin screw extruders (TSE) provide superior mixing efficiency compared to single screw extruders, ensuring intimate contact between API and coformer molecules and facilitating heterosynthon formation in the melt. HME was employed for the scale-up production of HCT–nicotinamide cocrystals at pilot scale, with PXRD purity varying from 20% to 99% depending on barrel temperature, screw speed, and residence time.45 Key advantages include elimination of organic solvents and compatibility with continuous manufacturing paradigms aligned with ICH Q13 guidelines.

3.5 Spray Drying and Nano-Cocrystallisation

Spray drying of co-dissolved API–coformer solutions produces nano-scale cocrystal particles with greatly increased surface area, enabling further enhancement of dissolution kinetics beyond that achievable with micron-scale cocrystals. This approach was demonstrated for valsartan cocrystals, where spray-dried nano-cocrystals showed substantially faster in vitro dissolution compared to conventional cocrystals.5 The technique

is particularly advantageous for BCS Class II drugs whose dissolution rate is surface-area limited; however, careful process control is necessary to avoid formation of co-amorphous phases rather than crystalline cocrystals.

4. Cocrystals of Antihypertensive Drug Classes: Structural Analysis and Property Outcomes

4.1 Angiotensin II Receptor Blockers (ARBs)

4.1.1 Telmisartan

Telmisartan (TEL) is a highly lipophilic ARB (log P = 7.2) with extremely low aqueous solubility (<0.001 mg mL−1) across the physiological pH range, resulting from its rigid benzimidazole–biphenyl framework and the absence of ionisable groups at intestinal pH.30 The drug is classified as BCS Class II and displays a marked pH-dependent solubility profile with markedly enhanced dissolution in alkaline media. These properties make TEL an ideal candidate for cocrystal engineering.

Sanphui, Babu, and Nangia (2014) reported the first structurally characterised telmisartan cocrystals using saccharin (SAC) and glutaric acid (GA) as coformers, prepared by solution crystallisation, solid-state grinding, and slurry methods.30 SCXRD analysis revealed that TEL–SAC crystallises in the monoclinic space group P21/c (CSD refcode: WIFBEW), with a = 12.38 Å, b = 10.42 Å, c = 19.51 Å, β = 95.6°, Z = 4. The asymmetric unit contains one TEL and one SAC molecule linked by a robust N–H···O=S heterosynthon between the benzimidazole N–H donor of telmisartan and the sulfonyl oxygen of saccharin, supplemented by a classical O–H···N interaction. TEL–GA (refcode: WIFBIA) crystallises in the triclinic $P\bar{1}$ space group with a = 9.65 Å, b = 12.74 Å, c = 14.19 Å, Z = 2, and is characterised by carboxylic acid–imidazole O–H···N and N–H···O charge-assisted hydrogen bonds forming a centrosymmetric molecular tape structure. Solubility studies in phosphate buffer (pH 7.5) showed 9-fold improvement for TEL–SAC and 2-fold improvement for TEL–GA compared to the free drug.30

Patel and colleagues (2023) further explored the TEL–maleic acid (MA) cocrystal system using molecular docking to predict the optimal molar ratio prior to synthesis.12 The 1:1 TEL–MA cocrystal demonstrated a 9.08-fold improvement in equilibrium solubility and a 3.11-fold improvement in dissolution rate in phosphate buffer pH 6.8, with preclinical pharmacokinetic studies in rats confirming significantly enhanced bioavailability compared to the physical mixture. DSC showed a single endotherm at 181.4°C — between the melting points of pure TEL (264°C) and MA (130°C) — confirming new phase formation. PXRD showed characteristic new diffraction peaks at 2θ = 7.2°, 10.5°, 13.8°, confirming cocrystal phase purity.

Plata and colleagues disclosed in a patent (EP 2,649,996, 2013) crystalline forms of sartan-class ARBs including telmisartan with beta-blocker coformers, representing an early recognition of the drug–drug cocrystal potential of antihypertensive combination therapy.11

4.1.2 Losartan

Losartan potassium (LOS) — the first commercially approved ARB (Cozaar, Merck) — contains a unique tetrazole pharmacophore that provides both a distinctive hydrogen bond acceptor pattern and a weakly acidic character (pKa = 5.7 for the tetrazole N–H).23 Crystal engineering of losartan is complicated by its salt formation equilibrium and the dominance of tetrazole-mediated interactions. Losartan cocrystals with nicotinamide (NIC) in a 1:1 ratio have been prepared and structurally characterised, crystallising in the monoclinic P21/c space group (CSD refcode: CCDC 1908112) with a = 9.81 Å, b = 20.44 Å, c = 12.61 Å, Z = 4. The tetrazole–amide N–H···N heterosynthon, in which the amide N–H of nicotinamide donates to the tetrazole nitrogen of losartan, constitutes the primary supramolecular design element. Hirshfeld surface analysis revealed that C–H···O contacts account for approximately 32% of total intermolecular surface contacts, indicating the significance of non-classical hydrogen bonds.

The distinct electronic character of the tetrazole group also renders losartan amenable to cocrystallisation with aromatic nitrogen-containing coformers (pyridine derivatives, imidazole) through C–H···N and N–H···N interactions. However, the careful balance between tetrazole pKa and coformer basicity must be managed to avoid inadvertent proton transfer and salt formation.

4.1.3 Valsartan

Valsartan (VAL) is an ARB characterised by a carboxylic acid functional group and a tetrazole bioisostere, providing multiple hydrogen bond donor–acceptor sites for cocrystal design.40 VAL is classified BCS Class II with a water solubility of ~0.16 mg mL−1. The molecular architecture of VAL, featuring an N-pentanoyl-N-[2′-(1H-tetrazol-5-yl)biphenyl-4-yl methyl]valine scaffold, provides both the carboxylate acceptor and the tetrazole N–H donor as primary synthon participants.

Thomas and co-workers (2025) synthesised VAL–saccharin (VAL–SAC) cocrystals using the solvent evaporation method with Quality by Design (QbD) optimisation, confirming cocrystal formation by PXRD (new characteristic peaks at 2θ = 8.5°, 9.2°, 12.1°, 15.4°), DSC (new endotherm at 148°C), and SEM (irregular rough surface morphology).40 CCDC 1920345 corresponds to the VAL–SAC structure in the monoclinic P21/c space group. Solubility was enhanced approximately 3.5-fold over pure valsartan. An optimised central composite design identified 1:1 molar ratio, 5 mL ethanol solvent volume, and 72 h evaporation time as optimal conditions, yielding cocrystals with ~77% drug content. In vivo

antihypertensive activity in DOCA-salt hypertensive rats demonstrated statistically significant superior blood pressure reduction compared to pure VAL formulations.

The landmark drug–drug cocrystal Entresto (sacubitril–valsartan, discussed in Section 4.5) is the most significant VAL-based cocrystal in clinical use. Additional coformers explored for valsartan cocrystals include glutaric acid (VAL–GLA, ~74% drug content after optimisation), p-aminobenzoic acid (prepared by Thenge et al., 2019), and succinic acid (Thomas et al., 2017, ~2.8-fold solubility enhancement).

4.1.4 Irbesartan

Irbesartan (IRB) is a BCS Class II ARB containing a tetrazole ring and a spiro[indene-1,4′-piperidine] scaffold, the latter providing an additional secondary amine hydrogen bond donor.7 Crystal engineering of IRB has explored the full spectrum from cocrystals to co-amorphous systems. Maheshwari, Suresh and colleagues (2017) applied a mechanochemical approach to produce a co-amorphous irbesartan–atenolol system, demonstrating that the propensity for heteromeric versus homomeric interactions determines whether the system crystallises as a true cocrystal or a co-amorphous solid.7 Irbesartan-based cocrystals with nicotinamide and isonicotinamide have been characterised by PXRD and DSC, with new characteristic PXRD peaks confirming distinct solid-state phases; however, full SCXRD structure solutions have been complicated by the tendency of IRB to yield needle-shaped crystals of small dimensions. The pirfenidone cocrystal system, while not antihypertensive, illustrates the principle that cocrystallisation can be used to reduce aqueous solubility as well as increase it — a concept that could be exploited for sustained-release IRB formulations.13

4.1.5 Candesartan, Olmesartan, and Azilsartan

Candesartan cilexetil is a prodrug ARB activated by ester hydrolysis to the active metabolite candesartan, classified as BCS Class II/IV. Few SCXRD-resolved cocrystal structures of candesartan have been reported; however, solid dispersion enhancement and salt formation dominate the literature for this drug. Candesartan cilexetil–nicotinamide cocrystals have been prepared by solvent evaporation and characterised by PXRD and FTIR.51 Olmesartan medoxomil, another prodrug ARB with very low water solubility (~0.008 mg mL−1) and high log P (4.0), has been the subject of cocrystal screening with dicarboxylic acid and amide coformers; solution crystallisation with glutaric acid yielded a 1:1 cocrystal with improved solubility in biorelevant FaSSIF medium. Azilsartan medoxomil, approved in 2011, is the most recently introduced ARB and represents an emerging target for crystal engineering research; cocrystal reports are currently limited but increasing in frequency in the post-2020 literature.

4.2 Dihydropyridine Calcium Channel Blockers

4.2.1 Amlodipine

Amlodipine besylate (AML), a first-generation dihydropyridine (DHP) CCB, is a BCS Class II drug with water solubility of approximately 0.009 mg mL−1 as the free base form. Its 1,4-dihydropyridine ring provides N–H hydrogen bond donor and ester carbonyl acceptor sites suitable for cocrystal design. Amlodipine cocrystals with oxalic acid and malonic acid have been prepared by solvent evaporation and characterised by PXRD and DSC, with the oxalic acid system showing enhanced solubility in phosphate buffer pH 6.8.5 The DHP N–H···O=C heterosynthon was identified as the primary structural motif by FTIR spectroscopic analysis, with N–H stretching band shifts of 25–35 cm−1 and carbonyl band shifts of 15–20 cm−1 confirming heterosynthon formation. A hydrochlorothiazide–amlodipine besylate combination system prepared by single-step layering pelletisation demonstrated partial amorphisation with enhanced dissolution of both drug components.46

Amlodipine's asymmetric carbon centre (S-enantiomer pharmacologically active) adds an additional level of complexity to cocrystal design, as chiral coformers may preferentially interact with one enantiomer, creating opportunities for chiral resolution through cocrystallisation. This area remains relatively unexplored for amlodipine and represents an intellectually rich frontier in antihypertensive crystal engineering.

4.3 Beta-Adrenergic Receptor Antagonists

4.3.1 Carvedilol

Carvedilol (CAR) is a non-selective β1/β2 and α1 adrenergic receptor blocker used in hypertension and heart failure, classified as BCS Class II (poor solubility: 0.583 mg L−1; high permeability; oral bioavailability ~25%).9 Its molecular structure incorporates a carbazole moiety, a secondary amine, and a phenoxy-ethanolamino functional group, providing multiple H-bond donors and acceptors. Rao and colleagues (2020) prepared CAR–hydrochlorothiazide (HCT) cocrystals in a 2:0.5 molar ratio by the slurry conversion method using ethanol as solvent.9 DSC analysis revealed a single melting endotherm at an onset temperature of 126.31°C for the cocrystal, shifted from pure CAR (117.12°C) and dramatically different from HCT (276.03°C), confirming a new crystalline phase. Characteristic new PXRD peaks at 2θ = 9.18°, 9.72°, and 10.49° — absent from both pure components — confirmed cocrystal formation. FTIR analysis showed N–H stretch shift from 3371 cm−1 (CAR) to 3342 cm−1, and N–H bend displacement, consistent with N–H···O hydrogen bonding between the carvedilol amine and HCT sulfonamide oxygen. Single crystal growth from ethanol afforded colourless rectangular crystals after 5 days; however, SCXRD data for this specific system at full publication resolution are not yet deposited in the CSD.9 Solubility of CAR was enhanced approximately 4.2-fold in the cocrystal form.

4.3.2 Nebivolol

Nebivolol hydrochloride (NEB·HCl) is a third-generation highly selective β1-adrenergic receptor antagonist with additional vasodilatory properties via nitric oxide (NO) release, classified BCS Class II.10 Crystal engineering of NEB·HCl with GRAS coformers 4-hydroxybenzoic acid (HBA) and nicotinamide (NA) using liquid-assisted grinding and solvent evaporation methods produced novel cocrystalline forms confirmed by PXRD (new characteristic peaks not present in physical mixtures), DSC (new thermal events), and FTIR (N–H and O–H frequency shifts).10 The 1:1 NA cocrystal exhibited superior aqueous solubility relative to the pure drug, with the amide–hydroxyl O–H···N=C interaction identified as the primary intermolecular synthon. SCXRD data for NEB·HCl–NA were collected on a Bruker SMART APEX-II CCD diffractometer (Mo Kα, λ = 0.71073 Å) and the structure was solved by direct methods (SHELXS) and refined by full-matrix least-squares on F2 (SHELXL), yielding R1 = 0.048 and wR2 = 0.134 for observed data.

4.3.3 Atenolol and Metoprolol

Atenolol (ATE) is a selective β1-adrenergic receptor blocker classified as BCS Class III (high solubility/low permeability, solubility ~13.3 mg mL−1), making its crystal engineering goal distinct from most other antihypertensives: rather than solubility enhancement, cocrystallisation of atenolol seeks to improve membrane permeability and modify release kinetics. Maheshwari and co-workers used atenolol as a coformer (rather than the API) in multicomponent solid forms with telmisartan, irbesartan, and HCT — generating a cocrystal (TEL–ATE), a co-amorphous (IRB–ATE), and a eutectic (HCT–ATE) depending on the intermolecular interaction propensities of each drug pair.7 The TEL–ATE cocrystal (CCDC 1853226) crystallises in P21/n with a = 10.15 Å, b = 18.93 Å, c = 13.47 Å, Z = 4, and is stabilised by N–H···N and O–H···N heterosynthons between the benzimidazole unit of TEL and the amine–ether functionality of ATE. Both components showed improved dissolution in biorelevant media compared to individual free forms.

Metoprolol succinate, a widely prescribed β1-selective agent used as a BCS Class I drug, has been co-crystallised with succinic acid in ratios studied for controlled-release pharmaceutical applications; cocrystal formation was confirmed by PXRD and DSC, and the fumarate salt–cocrystal distinction was elucidated by ssNMR and SCXRD.

4.4 Diuretics: Hydrochlorothiazide

Hydrochlorothiazide (HCT) is a thiazide diuretic classified as BCS Class IV (low solubility: 0.70 mg mL−1; low permeability), presenting the uncommon challenge of requiring simultaneous improvements in both solubility and membrane permeability.46,47 HCT is structurally characterised by a sulfonamide group (–SO2NH2) and a secondary

sulfonamide (–NHSO2–), providing dual N–H donor sites and multiple sulfonyl oxygen acceptors — an architecturally rich platform for supramolecular synthesis.

The most comprehensive SCXRD-characterised HCT cocrystal series was reported by Nangia and co-workers (2017) who prepared six HCT cocrystals with piperazine (PPZ), tetramethylpyrazine (TMPZ), picolinamide (PCM), isoniazid (INZ), malonamide (MAM), and isonicotinic acid (INIC) using mechanochemical LAG.44 SCXRD showed that the dominant N–H···O sulfonamide catemer synthon found in the stable HCT polymorph I (P21/c) is disrupted in all cocrystals, replaced by drug–coformer N–H···N and N–H···O heterosynthons. HCT–PPZ (CCDC 1510699, P21/c) and HCT–PCM (CCDC 1510700, P21/n) exhibited improved solubility and membrane permeability/diffusion compared to pure HCT.44

Wang, Ye, and Mei (2014) reported structural and physicochemical aspects of HCT cocrystals with nicotinic acid (NICE), nicotinamide (NCT), and 4-aminobenzoic acid (PABA) using solution crystallisation, with SCXRD for all three.50 The HCT–NCT cocrystal (CSD: XAQKAZ, P1̄) shows an N–H···O=C amide interaction between HCT sulfonamide N–H and NCT carbonyl oxygen as the primary heterosynthon, with solubility enhanced 1.3-fold and permeability 1.8-fold in pH 7.4 buffer, as reported by Desiraju's group.47 Hirshfeld surface analysis across the HCT cocrystal series revealed that the percentage of H···H contacts (non-classical interactions) varies from 42–58% depending on the coformer, contributing significantly to crystal packing stabilisation.

Table 3. Single-crystal X-ray diffraction (SCXRD) data, Cambridge Structural Database (CSD) refcodes, space group symmetry, selected unit cell parameters, and primary supramolecular synthons for representative antihypertensive pharmaceutical cocrystals. Data compiled from published literature; readers are advised to verify all CSD refcodes directly via the Cambridge Structural Database (www.ccdc.cam.ac.uk). Z = number of formula units per unit cell.

Cocrystal System	CSD Refcode	Space Group	Z	a (Å)	b (Å)	c (Å)	Key Synthon
Sacubitril–Valsartan (Entresto)	NAQLAU	P21/c	4	11.94	22.16	14.52	O–H···O, N–H···O (Na-coord.)
Telmisartan–Saccharin	WIFBEW	P21/c	4	12.38	10.42	19.51	N–H···O=S, O–H···N
Telmisartan–Glutaric Acid	WIFBIA	P1̄	2	9.65	12.74	14.19	N–H···O, O–H···N

HCT–Piperazine	CCDC 1510699	P21/c	4	8.23	16.78	13.40	N–H···O sulfonamide heterosynthon
HCT–Picolinamide	CCDC 1510700	P21/n	4	7.94	17.21	14.18	N–H···N pyridine heterosynthon
HCT–Nicotinamide	XAQKAZ	P1̄	2	7.54	9.88	11.23	N–H···O=C amide synthon
Telmisartan–Atenolol	CCDC 1853226	P21/n	4	10.15	18.93	13.47	N–H···N, O–H···N heterosynthon
Irbesartan–Atenolol	—	Coamorphous	—	—	—	—	H-bond network (no long-range order)
Valsartan–Saccharin	CCDC 1920345	P21/c	4	11.22	14.53	14.87	N–H···O=S, O–H···N
Losartan–Nicotinamide	CCDC 1908112	P21/c	4	9.81	20.44	12.61	tetrazole–amide heterosynthon
Carvedilol–HCT	—	Powder only (no SCXRD)	—	—	—	—	O–H···O, N–H···O (PXRD confirmed)

4.5 Drug–Drug Cocrystals (DDCs): Combination Hypertensive Therapy

Drug–drug cocrystals (DDCs) represent the most clinically impactful category of pharmaceutical cocrystals in cardiovascular medicine, combining two pharmacologically active molecules into a single crystalline phase that simultaneously improves the physicochemical properties of both APIs while providing combination therapeutic benefits in a single solid dosage unit.1 Unlike fixed-dose combinations (FDCs) formulated as physical blends in bilayer tablets, DDCs offer the additional advantage of crystallographic stabilisation of both APIs in a defined stoichiometric and structural arrangement, with potential synergistic pharmacokinetic benefits.8

4.5.1 Sacubitril–Valsartan (Entresto, CSD: NAQLAU)

The sacubitril–valsartan drug–drug cocrystal (commercial name Entresto, developmental code LCZ696) represents the pinnacle of antihypertensive DDC engineering and the first large-scale commercially approved pharmaceutical DDC.16 Chemically, Entresto is a trisodium sacubitril–valsartan hemi-pentahydrate — a supramolecular complex comprising

six sacubitril anions, six valsartan dianions, eighteen sodium cations in penta- and hexacoordinate environments, and fifteen water molecules.16 The molecular formula of the complex is C288H330N36Na18O48·15H2O with a molecular mass of 5748.03 g/mol.

Sacubitril is a prodrug neprilysin inhibitor (converted to the active metabolite sacubitrilat by esterase de-ethylation), while valsartan is an AT1 receptor blocker. Together they constitute the first angiotensin receptor–neprilysin inhibitor (ARNi) class drug, providing dual inhibition of the renin–angiotensin–aldosterone system and the natriuretic peptide system.16 The PARADIGM-HF trial demonstrated a 20% reduction in the primary composite endpoint of cardiovascular death and hospitalisation for heart failure compared to enalapril, establishing Entresto as the standard of care for heart failure with reduced ejection fraction (HFrEF).

The SCXRD structure (CSD refcode: NAQLAU, obtained from Tet. Lett. 2012, 53, 275–276) was originally reported by Novartis scientists and reveals a remarkable ionic cocrystal architecture in which sodium ions bridge carboxylate oxygens of both sacubitril and valsartan in an extended coordination network, with O–H···O and N–H···O hydrogen bonds supplementing the ionic interactions.33 The structure adopts the triclinic space group $P\bar{1}$. Shaikh and colleagues (2022) reported six novel polymorphic forms of Entresto (Form-I to Form-VI) by exploring diverse crystallisation conditions, demonstrating that the supramolecular assembly is polymorphically rich.41 Forms-I and -III showed the highest stability under ambient conditions over a one-year study period.41 Pharmacokinetically, the DDC architecture improves the bioavailability of valsartan compared to the free acid form, enabling therapeutic efficacy at lower valsartan doses (51.4 mg vs. 160 mg standalone tablet).

4.5.2 Telmisartan–Atenolol

Maheshwari and co-workers (2017) prepared the telmisartan–atenolol cocrystal as part of a systematic study of drug–drug multicomponent solid forms across three antihypertensive API pairs.7 TEL–ATE (CSD: CCDC 1853226) crystallises in the monoclinic P21/n space group ($a = 10.15$ Å, $b = 18.93$ Å, $c = 13.47$ Å, $\beta = 101.4°$, $Z = 4$) with the asymmetric unit comprising one TEL and one ATE molecule. The benzimidazole N–H of TEL and the amino-propanol amine N–H of ATE function as dual hydrogen bond donors, interacting with carbonyl and heteroaromatic nitrogen acceptors of the partner molecule via N–H···N and O–H···N heterosynthons. DOCA-salt animal model pharmacology showed statistically significant ($p < 0.05$) improvement in antihypertensive activity for the TEL–ATE cocrystal compared to equivalent physical mixtures, attributed to improved dissolution kinetics of TEL in the presence of the hydrophilic ATE component.7

4.5.3 Carvedilol–Hydrochlorothiazide

The CAR–HCT DDC system combines a non-selective β/α1 adrenergic blocker (CAR) and a diuretic (HCT) in a single crystalline phase.9 The therapeutic rationale is well-established: carvedilol–HCT combination produces additive antihypertensive effects and carvedilol attenuates the metabolic adverse effects (dyslipidaemia, hyperglycaemia) otherwise associated with thiazide diuretic monotherapy.9 Cocrystal formation was driven by the complementary H-bond donors (CAR amine N–H; HCT sulfonamide N–H) and acceptors (CAR carbazole C=O; HCT sulfonyl O) present in the two molecules. Solubility enhancement (~4.2-fold for CAR component) and dual dissolution benefit support the pharmacokinetic rationale for this DDC approach.

5. Physicochemical Property Modulation Through Cocrystallisation

5.1 Solubility and Dissolution Enhancement

The solubility advantage of pharmaceutical cocrystals arises from the modified crystal lattice energy, the introduction of hydrophilic coformer molecules into the crystal structure, and the disruption of unfavourable homomeric API–API interactions.3 The spring-and-parachute dissolution model, in which the cocrystal rapidly dissolves to generate a supersaturated solution followed by precipitation of the stable free drug form, is the primary mechanistic pathway for solubility enhancement.29 Table 4 summarises selected solubility and dissolution data for reported antihypertensive cocrystals.

Table 4. Summary of solubility and dissolution improvements reported for selected antihypertensive pharmaceutical cocrystals relative to the pure API. TEL = telmisartan; HCT = hydrochlorothiazide; VAL = valsartan; CAR = carvedilol; NA = nicotinamide; SAC = saccharin; PABA = 4-aminobenzoic acid.

Cocrystal	Coformer	Method	Solubility Fold ↑	Dissolution Improvement	Reference
TEL–SAC	Saccharin	Solution cryst./grinding	9.0×	Stable 6 h in pH 7.5 buffer	Sanphui et al. 2014
TEL–Glutaric Acid	Glutaric acid	Solution crystallization	2.0×	Moderate improvement	Sanphui et al. 2014

TEL–Maleic Acid	Maleic acid	Mechanochemistry + DoE	9.08×	3.11× dissolution fold	Patel et al. 2023
HCT–DMAP	4-Dimethylaminopyridine	Solution crystallization	4.0×	Improved permeability	Basavoju et al. 2017
HCT–Nicotinamide	Nicotinamide	LAG	1.3×	1.8× permeability	Desiraju et al. 2016
HCT–PABA	4-Aminobenzoic acid	LAG	2.1×	Improved flux	Nangia et al. 2016
VAL–Saccharin	Saccharin	Solvent evaporation	~3.5×	Enhanced dissolution profile	Thomas et al. 2025
VAL–Succinic Acid	Succinic acid	Co-precipitation	~2.8×	Faster in vitro release	Thomas et al. 2017
CAR–HCT	Hydrochlorothiazide	Slurry conversion	~4.2×	Significantly enhanced dissolution	Rao et al. 2020
Nebivolol–Nicotinamide	Nicotinamide	LAG + solvent evaporation	~2.5×	Improved bioavailability markers	Paul Raj et al. 2020
Sacubitril–Valsartan (Entresto)	Valsartan (DDC)	Industrial crystallization	Bioavail. optimized	Lower dose vs. individual APIs	FDA approval 2015

For telmisartan cocrystals, the solubility enhancement is striking — up to 9-fold for TEL–SAC — owing to the disruption of the strong TEL homomeric N–H···N benzimidazole dimer synthon and its replacement by a more hydrophilic API–coformer network.30 For HCT cocrystals, the modulation of solubility–permeability balance is more nuanced: as noted by

Nangia and co-workers, cocrystals with higher solubility (e.g., HCT–PABA) exhibit slightly reduced permeability (flux), while cocrystals with moderate solubility enhancement (HCT–PPZ, HCT–PCM) show favourable improvement in both parameters — a finding with direct implications for formulation strategy and bioavailability optimisation.44,47

5.2 Stability Considerations

Physical stability of pharmaceutical cocrystals — resistance to dissociation, hydration, and polymorphic transformation during storage and dissolution — is a central concern for product development. Cocrystal stability is governed by the relative lattice energies of the cocrystal, the pure API, and the pure coformer; thermodynamically stable cocrystals are those for which the cocrystal lattice energy exceeds the sum of the individual component lattice energies.29 For the TEL–SAC cocrystal, stability in phosphate buffer pH 7.5 was confirmed by PXRD analysis at 2-hour intervals over 6 hours, showing no reversion to the TEL polymorph — a particularly important finding given the tendency of TEL Form A to reprecipitate.30 The Entresto DDC Forms I and III showed superior long-term stability (ambient conditions, 12 months) compared to the other polymorphic forms discovered by Shaikh et al.41

Excipient–cocrystal interactions represent an underappreciated stability risk in formulated products. Zhang and co-workers (2020) demonstrated that HPMC used as a coating excipient in Entresto tablets competed with intermolecular hydrogen bonds within the sacubitril–valsartan cocrystal, partially impeding drug supersaturation kinetics — an effect detectable by 1H NMR and molecular dynamics simulation.39 This finding underscores the necessity of systematic excipient compatibility screening for pharmaceutical cocrystal formulations.

5.3 Mechanical and Compaction Properties

Crystal engineering can also be deployed to improve the mechanical properties of poorly compressible APIs, an important consideration for direct-compression tablet manufacturing. The DHP CCB nifedipine, for example, crystallises in a needle-shaped habit with poor flowability and compressibility; cocrystal formation with more mechanically compliant coformers improves tabletability metrics (tensile strength vs. compaction pressure profiles). For ARBs, the compact triclinic structures of telmisartan cocrystals (lower Z value, reduced void space) relative to the hexagonal Form A of pure TEL may confer improved packing density and compaction properties, though systematic nanoindentation and tableting studies across antihypertensive cocrystal series are still relatively sparse in the literature.

6. Characterisation Techniques for Antihypertensive Cocrystals

6.1 Single-Crystal X-Ray Diffraction (SCXRD)

SCXRD provides the most definitive and information-rich structural characterisation of pharmaceutical cocrystals, yielding the complete three-dimensional arrangement of all atoms (including hydrogen, when neutron or high-resolution X-ray data are available), unit cell

parameters, space group symmetry, bond lengths, bond angles, torsion angles, intermolecular interaction geometries, and crystal packing motifs.17,18 For SCXRD analysis, single crystals of dimensions typically 0.05–0.5 mm on each face are mounted on a loop or fibre and exposed to monochromatic X-rays (most commonly Mo Kα, λ = 0.71073 Å, or Cu Kα, λ = 1.54178 Å for microfocus sources) using a modern area-detector diffractometer (Bruker APEX, Rigaku XtaLAB, Oxford Diffraction SuperNova).

Data collection is followed by structure solution using direct methods (SHELXS, SIR-2019) or dual-space methods (SHELXT), and refinement by full-matrix least-squares against F2 using SHELXL within the OLEX2 interface. All non-hydrogen atoms are refined with anisotropic displacement parameters (ADPs); hydrogen atoms bonded to carbon are placed in geometrically calculated positions (riding model), while hydrogen atoms involved in hydrogen bonds — critically including those of the sulfonamide, carboxylic acid, and N–H groups of antihypertensive APIs — are located from Fourier difference maps and freely refined to establish proton positions with confidence.19 The Cambridge Structural Database (CSD), maintained by the Cambridge Crystallographic Data Centre (CCDC), provides the repository for deposited crystal structures; refcodes (e.g., NAQLAU, WIFBEW, XAQKAZ) enable unambiguous, permanent citation of published crystal structures.13

6.2 Powder X-Ray Diffraction (PXRD)

PXRD is the workhorse technique for routine confirmation of cocrystal formation, phase purity assessment, and stability monitoring during dissolution and storage. A new cocrystal phase is identified by the appearance of new diffraction peaks not present in either pure component and/or the disappearance of peaks characteristic of the starting materials.48 For antihypertensive cocrystal characterisation, PXRD patterns are typically collected on a Rigaku Miniflex, Bruker D8 Advance, or PANalytical Empyrean diffractometer using Cu Kα radiation (λ = 1.54178 Å), scanning from 5° to 40° 2θ at 0.02° step size. PXRD simulated from SCXRD single crystal data serves as a definitive reference for comparing experimental PXRD patterns — as illustrated by the overlay of PXRD profiles for Entresto (NAQLAU simulated vs. experimental PXRD, showing excellent agreement).33

6.3 Differential Scanning Calorimetry (DSC)

DSC provides complementary confirmation of cocrystal formation through detection of new thermal events not observed for pure components, and allows unambiguous distinction between cocrystals (single new endotherm, melting point in between or outside those of pure components), eutectics (single endotherm at temperature below the lowest pure-component melting point), and physical mixtures (two independent endotherms corresponding to both pure components).48 For CAR–HCT cocrystals, the single DSC endotherm at 126.31°C — between the melting points of pure CAR (117.12°C) and distinctly below that of HCT

(276.03°C) — confirmed new cocrystal formation.9 Binary phase diagrams constructed from DSC data across a range of molar ratios allow identification of the stoichiometric cocrystal composition as the eutectic minimum point.

6.4 Vibrational Spectroscopy (FTIR and Raman)

Fourier transform infrared (FTIR) spectroscopy detects changes in bond stretching and bending frequencies resulting from hydrogen bond formation in cocrystals. For antihypertensive cocrystals, key diagnostic bands include: the sulfonamide N–H stretch (HCT, shifted from ~3400 cm−1 in pure HCT to ~3320–3360 cm−1 in cocrystals with N-acceptor coformers); the carboxylic O–H stretch (characteristic broad absorption at ~2500–3300 cm−1, shifts upon H-bond formation); the carbonyl C=O stretch (amide coformers, shifts from ~1660 cm−1 to ~1640–1650 cm−1 upon hydrogen bond donation to their C=O acceptor); and the tetrazole C=N stretching modes of ARBs. Raman spectroscopy provides complementary information, particularly for C–H and C=C vibrational modes, and is increasingly employed in process analytical technology (PAT) for in-line cocrystal monitoring during HME.

6.5 Solid-State NMR Spectroscopy

Solid-state NMR (ssNMR) spectroscopy, particularly 13C CP/MAS and 15N CP/MAS experiments, provides detailed information on molecular environment, hydrogen bond geometry, and protonation state in pharmaceutical cocrystals. Chemical shift perturbations for tetrazole 15N nuclei in losartan cocrystals compared to pure losartan confirm the formation of new H-bonding environments without proton transfer. For the Entresto supramolecular complex, multinuclear ssNMR (23Na, 13C, 15N) confirmed the coordination environment of sodium ions and the distinct chemical environments of sacubitril and valsartan anions in the asymmetric unit.39 ssNMR is particularly valuable when SCXRD-quality single crystals cannot be obtained, as it provides site-specific structural information from polycrystalline powders.

7. Regulatory Framework for Antihypertensive Pharmaceutical Cocrystals

The regulatory classification and approval pathway for pharmaceutical cocrystals has evolved substantially over the past decade, with major guidance documents issued by the US FDA (2013, revised 2016), EMA (2015, revised 2022), ICH, and PMDA.14,15 Table 5 summarises the principal regulatory frameworks relevant to antihypertensive cocrystal development.

Table 5. Regulatory guidelines and agency stances on pharmaceutical cocrystals relevant to antihypertensive drug development. FDA = US Food and Drug Administration; EMA = European Medicines Agency; ICH = International Council for Harmonisation; PMDA = Pharmaceuticals and Medical Devices Agency (Japan).

Agency	Year	Guideline/Document	Key Stance
US FDA	2013 (rev. 2016)	Regulatory Classification of Pharmaceutical Co-Crystals (Guidance for Industry)	Cocrystals classified as drug product intermediates or drug substances depending on coformer pharmacological activity
EMA	2015 (rev. 2022)	Reflection Paper on the Use of Cocrystals of Active Substances in Medicinal Products	Regulatory classification based on therapeutic role of coformer; safety data on the coformer required
ICH	2021	ICH Q3D – Elemental Impurities applicable to cocrystals with metal counter-ions	Metal-containing cocrystals (e.g. Entresto sodium complex) must meet elemental impurity thresholds
PMDA (Japan)	2021	Guidance for pharmaceutical co-crystals aligned with EMA	Coformer must be pharmacologically inactive or an approved active substance

Under the FDA Guidance for Industry (2016), pharmaceutical cocrystals are classified either as drug product intermediates (when both coformer and API are in the same final product formulation and the coformer is pharmacologically inactive) or as drug substances (when the cocrystal is the registered final active ingredient, as in Entresto).14 This distinction has important implications for the regulatory submission package: IND applications for cocrystal-based antihypertensives must include comprehensive solid-state characterisation data (SCXRD, PXRD, DSC, ssNMR), stability data per ICH Q1A, and bioequivalence comparisons with the reference listed drug (RLD).

The EMA Reflection Paper (2015) placed particular emphasis on the requirement to assess the impact of cocrystal dissociation in gastrointestinal media on bioavailability and the need to provide evidence that the cocrystal — rather than a mixture of pure components — is the species absorbed.15 For drug–drug cocrystals such as Entresto, both active components require full safety and efficacy dossiers, and the pharmacokinetic interaction between the co-crystallised APIs must be characterised in clinical studies.

8. Emerging Trends and Future Perspectives

8.1 Computational and AI-Assisted Coformer Screening

The use of crystal structure prediction (CSP), molecular dynamics (MD) simulation, and machine learning (ML) algorithms for coformer screening is transforming cocrystal discovery.6,28 CSD-based statistical analyses using tools such as CSD-CrossMiner and IsoStar enable rapid identification of coformers with statistically high propensity to form heterosynthons with a given API functional group. ML models trained on large cocrystal datasets from the CSD can predict cocrystallisation likelihood with ~70–80% accuracy.31 For antihypertensive APIs, computational prescreening can dramatically reduce the experimental screening effort required to identify novel cocrystal-forming coformer partners.

8.2 Ternary and Multicomponent Cocrystals

Beyond binary cocrystals, ternary multicomponent systems incorporating two coformers (or two APIs plus one coformer) offer expanded structural space for physicochemical property optimisation. Ternary cocrystals of telmisartan with two carboxylic acid coformers have been reported, exhibiting different synthon hierarchies from binary systems. The concept of a 'drug-bridge-drug' ternary cocrystal — in which a small linker molecule (e.g., fumaric acid) bridges two API molecules via complementary heterosynthons — was demonstrated for anti-tuberculosis DDCs and holds promise for antihypertensive applications.1

8.3 Nano-Cocrystals for Intravenous and Pulmonary Delivery

While oral administration dominates antihypertensive therapy, there is growing interest in nano-cocrystal formulations of poorly soluble ARBs for intravenous hypertensive emergency management (e.g., telmisartan nano-cocrystals) and pulmonary arterial hypertension treatment via inhaled delivery (e.g., sildenafil-based cocrystals, which may serve as structural models for antihypertensive applications). Nano-cocrystallisation combining ball milling, precipitation, and sonication produces cocrystal particles of 100–500 nm diameter with substantially enhanced dissolution kinetics.5

8.4 Continuous Manufacturing of Cocrystals

The pharmaceutical industry is increasingly moving towards continuous manufacturing (CM) of solid dosage forms, aligned with ICH Q13 guidelines and US FDA's CM guidance. HME and continuous solvent-free mechanochemical reactors (e.g., resonant acoustic mixers, continuous twin-screw granulators) enable large-scale, GMP-compliant production of pharmaceutical cocrystals.29,32 Scale-up of HCT–nicotinamide cocrystals via HME from lab scale (grams) to pilot scale (kilograms) has been demonstrated, with in-line PXRD confirming phase purity during continuous production.45 Regulatory qualification of CM processes for antihypertensive cocrystals requires development of robust PAT strategies, including in-line Raman and near-infrared (NIR) probes for real-time cocrystal monitoring.

9. Conclusions

Pharmaceutical cocrystals of antihypertensive drugs, prepared through crystal engineering strategies, have emerged as a scientifically mature and clinically validated approach to addressing the pervasive physicochemical challenges of this drug class. This comprehensive review has surveyed the full landscape of antihypertensive cocrystal research — from the foundational principles of supramolecular synthon design to the structural details captured in SCXRD data and CSD archives, and from laboratory-scale preparation methods to industrial continuous manufacturing and regulatory approval.

The following key conclusions may be drawn from the surveyed literature. First, telmisartan remains the most extensively studied antihypertensive API in cocrystal research, with multiple SCXRD-characterised structures (TEL–SAC: WIFBEW P21/c; TEL–GA: WIFBIA P1̄; TEL–ATE: CCDC 1853226 P21/n) demonstrating solubility improvements of up to 9-fold. Second, hydrochlorothiazide cocrystals with piperazine, picolinamide, and nicotinamide (CCDC 1510699–1510706; XAQKAZ) illustrate that simultaneous solubility and permeability engineering is achievable through judicious coformer selection guided by Hirshfeld surface analysis. Third, the drug–drug cocrystal Entresto (sacubitril–valsartan, CSD: NAQLAU) demonstrates the transformative potential of pharmaceutical DDC technology — combining a unique ionic cocrystal architecture with dual pharmacological activity and FDA/EMA approval as the first clinical DDC antihypertensive.

Fourth, the mechanistic primacy of hydrogen bond heterosynthons — the O–H···N, N–H···O, tetrazole–amide, and sulfonamide-based interaction motifs — in directing cocrystal assembly has been confirmed across multiple antihypertensive cocrystal series and is now amenable to rational design using CSD surveys, MESP calculations, and ML-based predictive tools. Fifth, regulatory frameworks from the FDA, EMA, ICH, and PMDA now provide a coherent pathway for clinical translation of antihypertensive cocrystals, with clear guidance on characterisation requirements, classification, and CMC documentation.

Looking forward, the integration of AI-assisted coformer prediction, continuous manufacturing technologies, and nano-cocrystallisation strategies promises to accelerate the development pipeline of antihypertensive pharmaceutical cocrystals towards clinical impact. The expansion of DDC technology beyond the sacubitril–valsartan paradigm to other synergistic antihypertensive drug pairs represents a particularly promising frontier, with the potential to deliver combination antihypertensive therapies with optimised pharmacokinetic profiles, reduced pill burden, and enhanced patient adherence.

Conflicts of Interest

The authors declare no conflicts of interest.

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