Multidrug co-crystals: towards the development of effective therapeutic hybrids

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Co-crystals have garnered the interest of the pharmaceutical industry with the introduction of regulatory guidelines by the US Food and Drug Administration (FDA) as a result of expanded patent portfolios. The Phase II clinical success of tramadol and celecoxib co-crystal for the treatment of acute pain followed by a recent reflection paper published by the European Medicines Agency (EMA) have further boosted the development of drug–drug co-crystals. Here, we shed light on the developments of drug–drug co-crystals and highlight future perspectives for exploring new therapeutic hybrids deploying drug–drug, drug–nutraceuticals and drug–inorganic salt combinations with improved pharmaceutical and biopharmaceutical performance.

Introduction

The combination of multiple therapeutic agents into unit doses has become a popular drug development strategy, because monotherapy (i.e. targeting a specific receptor) is no longer considered effective in the management of many complex disorders, such as infectious diseases, HIV/AIDS, cancer, diabetes, and cardiovascular disease [1]. The use of cost-effective and multiple-targeting fixed-dose drug combinations (FDC) can help reduce pill load without the additional risk of adverse events or drug resistance, thereby improving patient compliance by simplified disease management. Drug combinations would also facilitate the reduction of managerial and manufacturing costs by reducing the outflow related to packaging and drug prescriptions. Fixed-dose combination products can comprise simple drug–drug combinations or drug–device combinations, such as drug-eluting stents or drug-biological products for use in cancer therapy. The advantages of FDC are often overshadowed because of various disadvantages, including issues with stability, and solubility differences and incompatibility between the parent drugs [2]. Therefore, it is necessary to develop alternative technologies and methodologies that facilitate the development of therapeutic hybrids to counter such problems.

An alternative to combining two or more drugs into a dosage form is the use of multicomponent solids, such as salts, mesoporous complexes, co-amorphous systems, and co-crystals, comprising two or more active pharmaceutical ingredients (APIs). Of all these types of system, co-crystals with expanded patent portfolios have garnered the interest of the pharmaceutical industry. The development of the first co-crystal can be traced back to 1844, when Wohler synthesized quinhydrone complex, which was later found to be a 1:1 co-crystal of quinone and hydroquinone [3]. According to the FDA, co-crystals are defined as ‘dissociable multi-component solid crystalline supramolecular complexes composed of two or more components within the same crystal lattice where in the components are in neutral state and interact via nonionic interactions’ [4].

The Phase II clinical success of tramadol and celecoxib co-crystal for the treatment of acute pain announced by ESTEVE Incorporation (http://www.esteve.es), followed by a recent reflection paper published by the EMA brought drug–drug co-crystals into the limelight [5]. Multidrug co-crystals (MDCs) with enhanced stability compared with co-amorphous systems [6] and reduced payload compared with
mesoporous and cyclodextrin complexes could find many applications in the development of novel systems. Here, we address the challenges and pitfalls in the development of MDCs [7]. We briefly outline the basic concepts related to drug-drug co-crystal development, screening strategies available, preparation methods, characterization tools, and evaluation parameters. We highlight future perspectives for exploring the possibilities of new therapeutic hybrids deploying drug–drug, drug–nutraceuticals, and drug–inorganic salt combinations with improved pharmaceutical and biopharmaceutical performance, with an emphasis on nanoscale co-crystals. To date, there is limited published work available on drug–drug co-crystals; the foundations from co-crystal development were extended to multidrug systems wherever appropriate, citing the available literature on drug–drug co-crystals.

**Multidrug co-crystals**

To date, multidrug co-crystals (MDCs) are undefined. Here, we have extended the definitions of co-crystals to MDC systems, and suggest that MDCs be defined as ‘dissociable solid crystalline supramolecular complexes comprising two or more therapeutically effective components in a stoichiometric ratio within the same crystal lattice, wherein the components may predominantly interact via nonionic interactions and rarely through hybrid interactions (a combination of ionic and nonionic interactions involving partial proton transfer and hydrogen bonding) with or without the presence of solvate molecules.’ The hybrid interactions in the proposed definition have been included because of the growing literature concerning salt/co-crystal hybrids and ionic co-crystals [8–14].

MDC could offer potential advantages of synergistic and/or additive effects [15–19], enhanced solubility and dissolution of at least one component [20–23], enhanced bioavailability [21], possible stabilization of unstable components through intermolecular interactions [24,25], and assistance in lifecycle management of existing products. Srinivasulu et al. reported an MDC comprising ethosuximide and gentamic acid that had an enhanced intrinsic dissolution rate (IDR). Both molecules are known for their anti-inflammatory activities and the reported MDC could find applications in the treatment of pain [20]. Cheney et al. developed a MDC comprising meloxicam and aspirin and reported a 12-times decrease in the time required to reach therapeutic concentrations, with a fourfold enhancement in bioavailability [21]. Palash et al. reported a MDC of curcumin with resorcinol and pyrogallol that had improved solubility. Dissolution rates were found to be 5 and 12 times faster for curcumin-resorcinol and curcumin-pyrogallol co-crystals respectively when compared to that of pure curcumin[22]. Zegarac et al. developed sildenafil and aspirin MDC with improved IDR compared with a marketed sildenafil citrate salt. The dual therapeutic effects displayed by this MDC might result from the antiplatelet activity of aspirin, suggesting its potential application in the treatment of erectile dysfunction in patients with cardiovascular complications [26]. Surov et al. developed a MDC of diflunisal and diclofenac with theophylline. The IDR of diclofenac-theophylline was around 1.2 times higher than for each drug alone. Enhanced hygroscopic stability of theophylline was observed at 100% relative humidity (RH) [27]. Different MDCs developed to date along with their preparation methods and applications are given in Table 1.

**Prediction and/or screening of MDC formation**

Currently, there is no published systematic computational approach for the development of MDCs. Predictions of co-crystal formation between drugs and coformers have been reported and can be successfully applied for the prediction of MDC formation. Prediction and/or screening can be done through knowledge-based approaches and experimental screening. Knowledge-based methods include synthesis engineering, use of molecular descriptors, hydrogen-bonding propensity and pKa-based models. These structure-based methods can successfully be applied to any two-molecule systems and, thus, could be used for drug-drug systems. Synthon engineering is one of the most widely used strategies to understand molecular interactions. It involves the identification of structural units within supermolecules that can be articulated and/or assembled to form intermolecular interactions by synthetic procedures; examples of frequently occurring synthons include carboxylic acid dimers, acid–pyridine, phenol–pyridine, and phenol–carboxylic acid [28]. Hydrogen-bonding interactions and synthon competition in organic crystals are often reported through analysis of the Cambridge Structural Database (CSD) [29]. Prashant et al. used a synthon-based retrosynthetic strategy to develop a MDC of lamivudine and zidovudine [30]. Synthon theory works well with simple molecules but is more complicated with molecules with multiple hydrogen-bond donors and acceptors [30,31]. Thus, several attempts have been made to develop new prediction models to optimize coformer selection. Fabian et al. proposed molecular complementarity as a criterion for predicting co-crystal formation [32]. The difference in lattice energy between the adduct and the reactants was suggested for prediction by Price and coworkers [33]. Delori et al. used hydrogen-bonding propensity calculations to predict the formation of a MDC of pyrimethamine with other drugs, such as carbamazepine and theophylline [31].

A simpler pKa-based prediction depicts that a salt is formed if the difference between the pKa base and pKa acid (ΔpKa) is >3, whereas a ΔpKa < 0 will generally result in the formation of a co-crystal [34]. By contrast, a ΔpKa of 0–3 can result in complexes containing proton-sharing or intermediate ionization states that can be assigned as salt/co-crystal hybrids [34–38]. In their work on theophylline–acid complexes, Childs et al. reported a 0 < ΔpKa < 2.5 region as a salt/co-crystal continuum zone [39]. After studying 6465 crystalline complexes in the CSD, and validating and quantifying the ΔpKa rule, Cruz Cabeza et al. recently reported a linear relation between ΔpKa and the possibility of proton transfer between acid–base pairs. They concluded that ΔpKa < −1 would exclusively result in a non-ionized complex; ΔpKa < 4 would result in an ionized complex; and between 1 ≤ ΔpKa ≤ 4, a 1 ΔpKa difference would increase the probability of proton transfer by 17% from 10% at ΔpKa = −1 to 95% at ΔpKa = 4. Cruz Cabeza et al. concluded that ΔpKa would be one of the most prominent and simplest methods to use to predict co-crystal formation [40].

The Hansen solubility parameter [41] has also been explored for the formation of single-drug co-crystals. Mohammad et al. proposed that considering unit components with similar Hansen solubility parameters would improve the co-crystal success rate [41]. Similarly, no experimental screening methodologies have been reported for MDC formation. Ternary phase diagrams based on solubility and melting [42–46] have been explored for single-drug
<table>
<thead>
<tr>
<th>Drug combination</th>
<th>CCDC Ref code</th>
<th>Therapeutic category</th>
<th>Method of preparation</th>
<th>Observations</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline–phenobarbital (2:1)</td>
<td>THOPBA</td>
<td>Antiasthmatic and sedative hypnotic</td>
<td>Distillation</td>
<td>Dissolution of theophylline and phenobarbital faster in pure powder than from co-crystal</td>
<td>[7]</td>
</tr>
<tr>
<td>Sulfadimidine–aspirin (1:1)</td>
<td>VUGMIT</td>
<td>Antibacterial and NSAID</td>
<td>Solvent evaporation</td>
<td>Pharmaceutical properties not evaluated</td>
<td>[28]</td>
</tr>
<tr>
<td>Sulfadimidine–4-ASA (1:1)</td>
<td>VUGMOZ</td>
<td>Antibacterial</td>
<td>Solvent evaporation</td>
<td></td>
<td>[28]</td>
</tr>
<tr>
<td>Theophylline–5-FU (2:1)</td>
<td>ZAYLOA</td>
<td>Antitubercular and anticancer</td>
<td>Heating at boiling point followed by instant cooling</td>
<td></td>
<td>[29]</td>
</tr>
<tr>
<td>Trimethoprim–sulfadimidine (1:1, 1:2)</td>
<td>RASSUZ</td>
<td>Antibacterial</td>
<td>Heating at boiling point followed by instant cooling</td>
<td></td>
<td>[30,31]</td>
</tr>
<tr>
<td>Trimethoprim–sulfamethoxy pyridazine (1:1)</td>
<td>QUASHEX</td>
<td>Antibacterial</td>
<td>Heating at boiling point followed by instant cooling</td>
<td></td>
<td>[32]</td>
</tr>
<tr>
<td>Tetroxoprim–sulfametrole (1:1)</td>
<td>IRIMEB</td>
<td>Antibacterial</td>
<td>Cogrinding and solvent evaporation</td>
<td>Physical conditions essential for isolating two distinct polymorphic forms via desolvation were established</td>
<td>[33,34]</td>
</tr>
<tr>
<td>Piracetam–genticic acid (1:1)</td>
<td>DAVPAS</td>
<td>Nootropic agent and NSAID</td>
<td>Co-grinding, slurry in water and solvent evaporation</td>
<td>Role determined of carboxylic acid–primary amide dimer in crystal engineering involving two APIs that are polymorphic in nature</td>
<td>[35]</td>
</tr>
<tr>
<td>Amoxicillin trihydrate–potassium clavulanate (3:7, 5:5, 7:3)</td>
<td>–</td>
<td>Antibacterial and β-lactamase inhibitor</td>
<td>Melting at 50°C for 30 min</td>
<td>No significant improvement in activity observed</td>
<td>[36]</td>
</tr>
<tr>
<td>Lamivudine–zidovudine (1:1)</td>
<td>COWSOX</td>
<td>Antiviral</td>
<td>Solvent evaporation</td>
<td>Established synthon theory as a model for prediction of co-crystals from single compound</td>
<td>[37]</td>
</tr>
<tr>
<td>Theophylline–genticic acid (1:1)</td>
<td>DUCROJ</td>
<td>Antiasthmatic and NSAID</td>
<td>Thermally assisted solvent evaporation</td>
<td>Pharmaceutical properties not evaluated</td>
<td>[38]</td>
</tr>
<tr>
<td>Ethenzamide–genticic acid (1:1)</td>
<td>QULLUF</td>
<td>Both drugs are NSAIDs, latter also has antitubercular properties</td>
<td>Solvent evaporation</td>
<td>Three polymorphic forms of ethenzamide and genticic acid identified with twofold increase in IDR</td>
<td>[20]</td>
</tr>
<tr>
<td>Sulfamethazine–theophylline (2:1)</td>
<td>AWJEW01</td>
<td>Antibacterial and antiasthmatic</td>
<td>Solvent evaporation</td>
<td>Thre polymorphic forms of ethenzamide and sulfamethazine co-crystal decreased compared with controls</td>
<td>[24]</td>
</tr>
<tr>
<td>Meloxicam–aspirin (1:1)</td>
<td>ARIFOX</td>
<td>NSAIDs</td>
<td>Solution crystallization, slurry and solvent drop grinding methods</td>
<td>44-fold increase in pH 7.4 phosphate buffer solubility along with improved C&lt;sub&gt;max&lt;/sub&gt;, MRT, AUC, and MAT. Bioavailability improved fourfold</td>
<td>[21]</td>
</tr>
<tr>
<td>Isoniazid–4-ASA (1:1)</td>
<td>URUDER</td>
<td>Antitubercular drugs</td>
<td>Solvent drop grinding</td>
<td>Rare case of simultaneous existence of pure hydrogen-bonded and partially ionic carboxylic acid/nitrogen-based dimers observed within the same crystal structure</td>
<td>[39]</td>
</tr>
<tr>
<td>Pyrazinamide–4-ASA (1:1)</td>
<td>URUGIY</td>
<td>Antitubercular drugs</td>
<td>Solvent drop grinding</td>
<td>Rare case of simultaneous existence of pure hydrogen-bonded and partially ionic carboxylic acid/nitrogen-based dimers observed within the same crystal structure</td>
<td>[39]</td>
</tr>
<tr>
<td>Carbamazepine–salicylic acid (1:1)</td>
<td>MOXWAY</td>
<td>Antiepileptic and anti-inflammatory</td>
<td>Unexpected in presence of moisture</td>
<td>Co-crystals formation mediated by water released by dibasic calcium phosphate dihydrate; detection of in situ co-crystal formation</td>
<td>[40]</td>
</tr>
<tr>
<td>Pyrazinamide–difuinusal (1:1)</td>
<td>–</td>
<td>Antitubercular and NSAID</td>
<td>Ball mill grinding</td>
<td>Density functional theory calculation used to study feasibility of co-crystal formation involving two APIs</td>
<td>[41]</td>
</tr>
<tr>
<td>Curcumin–pyrogallol (1:1)</td>
<td>AXOGIE</td>
<td>Anticancer</td>
<td>Liquid-assisted manual grinding</td>
<td>Dissolution rate 12 times faster than for curcumin alone</td>
<td>[22]</td>
</tr>
<tr>
<td>Aceclofenac–paracetamol (1:1)</td>
<td>–</td>
<td>NSAIDs</td>
<td>Various methods</td>
<td>Enhanced solubility of both drugs reported</td>
<td>[23]</td>
</tr>
<tr>
<td>Isoniazid–2-chloro-4-nitro benzoic acid (1:1)</td>
<td>LATLEZ</td>
<td>Antitubercular and antiviral compounds</td>
<td>Solvent evaporation</td>
<td>Pharmaceutical properties not evaluated</td>
<td>[42]</td>
</tr>
<tr>
<td>Piracetam–lithium chloride (1:1)</td>
<td>VEDDEP</td>
<td>Nootropic agent and mood-stabilizing agent</td>
<td>Solvent evaporation and grinding</td>
<td>Insignificant improvement in IDR reported</td>
<td>[14]</td>
</tr>
</tbody>
</table>
co-crystals and can be successfully applied to MDCs. Miscellaneous methods, such as liquid-phase excess enthalpy \((H_{ex})\) predictions [47], pulsed gradient spin-echo nuclear magnetic resonance (PGSE NMR) [48], and intermolecular site pairing energy (ISPE) [49], have been investigated for single-drug co-crystals, but require further validation before they are established as robust models for screening.

**Synthesis, characterization, and evaluation of MDC**

Generally, the preparation of MDCs does not differ from the conventional methods used in the preparation of co-crystals. Simple distillation, solvent evaporation, cooling crystallization, co-grinding and liquid-assisted grinding, slurry crystallization, melting, and sonic crystallization are a few of the techniques that have been used for the preparation of MDC (Table 1). Methods reported for the synthesis of co-crystals in general are outlined in Fig. 1 and all can be successfully applied for the preparation of MDC [50, 51].

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>CCDC Ref code</th>
<th>Therapeutic category</th>
<th>Method of preparation</th>
<th>Observations</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide–pentoxifylline (1:1)</td>
<td>FEYAS</td>
<td>Loop diuretic; the latter drug is used to treat intermittent claudication</td>
<td>Solvent evaporation</td>
<td>Pharmaceutical properties not evaluated</td>
<td>[43]</td>
</tr>
<tr>
<td>Pyrimethamine–carbamazepine (1:1)</td>
<td>KICWOK</td>
<td>Antimalarial and antiepileptic</td>
<td>Solvent evaporation</td>
<td>Heteroassociation between fluoroquinolones reported for first time</td>
<td>[44]</td>
</tr>
<tr>
<td>Pyrimethamine–theophylline (1:1)</td>
<td>KICWIE</td>
<td>Antimalarial and antiasthmatic</td>
<td>Solvent evaporation</td>
<td>Pharmaceutical properties not evaluated</td>
<td>[45]</td>
</tr>
<tr>
<td>Ciprofloxacin–norfloxacin (1:1)</td>
<td>KEXGAX</td>
<td>Antibacterial</td>
<td>Solution crystallization</td>
<td>Enhanced intrinsic dissolution rate observed compared with marketed product</td>
<td>[46]</td>
</tr>
<tr>
<td>Paracetamol–indomethacin and mefenamic acid (1:1)</td>
<td>–</td>
<td>NSAIDs</td>
<td>Solution crystallization</td>
<td>Enhanced physical stability and increased solubility observed</td>
<td>[26]</td>
</tr>
<tr>
<td>Sildenafil–aspirin</td>
<td>DISXOU</td>
<td>Antihypertensive and NSAID</td>
<td>Solvent drop grinding and solvent evaporation</td>
<td>Products showed enhanced stability and comparable dissolution rates</td>
<td>[27]</td>
</tr>
<tr>
<td>Diclofenac and Diffunisal–Theophylline (1:1)</td>
<td>–</td>
<td>Antiasthmatic and NSAID</td>
<td>Solvent drop grinding and solvent evaporation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapsone–sulfanilamide flavone, luteolin, caffeine and benzothiazolone (1:1)</td>
<td>–</td>
<td>Antiepileptic and antioxidants</td>
<td>Solution crystallization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine–ibuprofen</td>
<td>–</td>
<td>Antiepileptic and NSAID</td>
<td></td>
<td>Developed MDC using non-stoichiometric methods; pharmaceutical properties not evaluated</td>
<td>[47]</td>
</tr>
</tbody>
</table>

*Abbreviations: 4-ASA, 4-aminosalicylic acid; AUC, area under curve; MAT, mean absorption time; MRT, mean residence time.

Scale-up feasibility

There is scope for the scale up of MDC production, given that various methods have been recently reported for the scale up of single-drug co-crystals. Here, we discuss the scalable technologies that have been explored in single drug-based co-crystals, extending their applicability to MDC.

Spray drying has long been in use for the development of single-drug co-crystals and could be explored for the formation of MDC [54]. High shear granulation was used by Rehder et al. for the development of piracetam-tartaric acid co-crystals. The impeller speed, amount of granulating liquid, and the excipients used affected the co-crystal formation [55]. Dhumal et al. reported a scale up of an ibuprofen-nicotinamide co-crystal using hot melt extrusion up to 1 kg [56]. In their research, Daurio et al. manufactured caffeine–oxalic acid, nicotinamide–trans-cinnamic acid, carbamazepine–saccharin, and theophylline–citric acid co-crystals using twin screw extrusion (TSE) in quantities ranging from 20 g to 100 g [57]. They have also reported a further scale up of AMG 517–sorbic acid co-crystals using the TSE method in a similar batch size range (20–100 g). TSE-based co-crystals were found to be superior in terms of flow and stability compared with products developed using solution crystallization [58]. Solution
crystallization for scale up of co-crystals was attempted by Roy et al. for the synthesis of lamivudine with (S)-(−)-1,1′-Bi(2-naphthol)[(S)-(binol)] and by Daurio et al. for preparing AMG 517–sorbic acid co-crystals up to 15 kg [58,59]. Yu et al. explored the robustness of seeding-based cooling crystallization for the development of caffeine–glutaric acid co-crystals using first principles process modeling in a 10-L crystallizer [60]. Ende et al. recently explored resonance acoustic mixer-based synthesis of carbamazepine–nicotinamide co-crystals at a 22-g level using various solvents [61]. In their recent publication, Zhao et al. reported the use of a continuous oscillatory baffled crystallizer (COBC) for scalable co-crystallization of α-lipoic acid–nicotinamide using cooling crystallization and successfully developed co-crystal spherical agglomerates at a rate of 330 g/hour [62].

Process developments are likely to have a major role in producing a marketable MDC. Existing techniques, such as solvent-assisted crystallization methodologies, spherical co-crystallization technologies [58,62], and spray-drying technologies, could be...
successfully used for the bulk production of MDCs. Solvent-free processes, such as hot melt extrusion or twin screw extrusion systems, could serve as ecofriendly alternatives for the large-scale production of MDCs.

Regulatory views
Co-crystals have gained significant importance in the pharmaceutical industry with the introduction of regulatory guidelines. In 2013, the FDA was the first regulatory agency to publish guidance on the regulatory classification of co-crystals. This guidance was long awaited and was expected to boost the development of co-crystals, but it has in fact hampered their growth because of the classification of pharmaceutical co-crystals as ‘drug product intermediates’ rather than as new APIs; this was unexpected given that most of the coformers used for co-crystal development are pharmacologically inactive [4]. Recently, the EMA published a reflection paper on the use of co-crystals that considers pharmaceutical co-crystals for abridged applications. Co-crystals are given the status of ‘new active substances’ (NAS) if their safety and efficacy is proved [5]. Global regulatory requirements are still unclear for expanding the co-crystal market to the various regulated markets. It is unclear that how the FDA would treat applications related to MDC, but it is expected that the EMA guidelines would support the growth of an MDC market.

MDCs alter the pharmaceutical and biopharmaceutical properties of APIs without any chemical modification, and have the benefits of a crystalline solid form in that they provide a viable solution. Currently, there are very few marketed co-crystal products like Entresto (Sacubitril-Valsartan). Escitalopram oxalate containing N-protonated escitalopram cations along with charge-balancing oxalate dianions and N–H⋯O, O–H⋯O hydrogen bonds forming the supramolecular framework was found to be a salt/co-crystal hybrid [63]. Caffeine citrate [64] and sodium valproate [65] are two more examples of marketed products that are currently argued to be co-crystals.

Patent portfolios
A new patent in the pharmaceutical industry could mean longer exclusivity or even new exclusivity and would enhance the existing commercial value of a product. The essential criteria for the patentability of any invention are novelty, utility, and nonobviousness. Patent filing of MDCs is associated with their distinctive chemical compositions, supramolecular frameworks in crystal structure, and advantageous properties [66]. The precise nature
of these fundamental criteria varies according to the regional laws. For example, the European Patent Office (EPO) takes a ‘problem-and-solution’ for approach for determining the inventive step, whereas the United States Patent Office (USPTO) goes for a factual analysis to determine ‘nonobviousness’. Successful characterization of MDCs and the evaluation of their pharmaceutical and biopharmaceutical properties are prime considerations for effective patenting. The number of patents granted to MDCs and their methods of preparation are increasing annually. The commercialization potential, patentability of co-crystals, and patents granted to unit drug co-crystals have been discussed elsewhere [66,67]. Patent literature reporting the significant enhancement in solubility, dissolution rates, stability, bioavailability, and therapeutic efficacy of MDCs [15–19,68–74] is detailed in Table 2.

## Challenges involved

The systematic approach for dealing with the development of MDC is still unclear. Various synergistic combinations patented over the past few years reported the evaluation of the pharmaceutical and biopharmaceutical attributes of MDCs [15–19,68–73], such discussions are missing from much of the published MDC literature [31,75–83]. Most of the combinations reported were primarily focused on identifying hydrogen-bonding patterns, understanding the role of supramolecular interactions, and, to a certain extent, developing an appropriate combination for therapeutic application. One of the major challenges for designing MDCs is the selection of a pharmaceutically acceptable combination that could provide potential benefits. Exploring combinations of theophylline–phenobarbital [7], theophylline–5-fluorouracil (5FU) [78], pyrimethamine–carbamazepine and pyrimethamine–theophylline [31] might not provide any significant therapeutic benefits, with no supporting evidence for synergism or practical applications in therapy. Intervention of pharmacologists at this point would be vital to understand the mechanisms of individual drugs that produce desired therapeutic effects, to deal with dose adjustments, to study drug-drug interactions, and to explore possible therapeutic outcomes. Investigating the pharmacological outcomes of reported MDCs, such as piracetam–gentisic acid [84], lamivudine–zidovudine [30], etravirine–gentamic acid [20], sulfadimidine–acetylsalicylic acid and sulfadimidine–4-aminosalicylic acid [76], isoniazid and pyrazinamide with 4-aminosalicylic acid [85], piracetam–lithium chloride [14], furosemide–pentoxifylline, would also help in the development of an effective therapeutic hybrid. For example, in the theophylline–phenobarbital combination [7], theophylline is extensively metabolized by hepatic enzymes, whereas phenobarbital is a cytochrome P450 (CYP) inducer; thus, a decrease in theophylline levels below therapeutic concentrations is anticipated. It is also crucial to ensure that

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**TABLE 2**

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>Therapeutic category</th>
<th>Method of preparation</th>
<th>Remarks</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA–theanine</td>
<td>NSAID and psychoactive</td>
<td>Grinding and rota evaporation</td>
<td>Water-soluble aspirin for intravenous formulations</td>
<td>[92]</td>
</tr>
<tr>
<td>Cyproglinil–dithianon</td>
<td>Fungicides</td>
<td>Various methods</td>
<td>Synergistic effects observed in biological experiments</td>
<td>[91]</td>
</tr>
<tr>
<td>Duloxetine–naproxen</td>
<td>Antidepressant and NSAID</td>
<td>Cooling crystallization and cogrinding</td>
<td>Improved solubility, IDR, and bioavailability, thereby increasing dose response; decreased hygroscopicity and enhanced stability also observed</td>
<td>[85] [89]</td>
</tr>
<tr>
<td>Venlafaxine–celecoxib</td>
<td>Antidepressant and NSAID</td>
<td>Solvent crystallization</td>
<td>Improved solubility, IDR, and bioavailability, thereby increasing dose response; decreased hygroscopicity and enhanced stability also observed</td>
<td>[85] [89]</td>
</tr>
<tr>
<td>Ciprofloxacin and norfloxacin with various co-crystal forms</td>
<td>Antibacterial</td>
<td>Solvent drop grinding</td>
<td>Higher solubility, dissolution rates, and improved stability compared with parent compounds</td>
<td>[17]</td>
</tr>
<tr>
<td>Mesalamine with alpha amino acids, flavones, and nutraceuticals</td>
<td>Anti-inflammatory</td>
<td>Thermally assisted solvent evaporation and solvent drop grinding</td>
<td>Increased residence time and synergistic action reported</td>
<td>[16]</td>
</tr>
<tr>
<td>Metformin–oleoylethanolamide</td>
<td>Antidiabetic and antiobesity</td>
<td>Solvent drop grinding</td>
<td>Improved bioavailability with additional antiobesity action</td>
<td>[19]</td>
</tr>
<tr>
<td>Quercetin–metformin</td>
<td>Antioxidant and antidiabetic</td>
<td>Melting, solvent drop grinding</td>
<td>Improved solubility, IDR, stability, and great therapeutic potential obtained</td>
<td>[18]</td>
</tr>
<tr>
<td>Telmisartan–beta blockers</td>
<td>Antihypertensive</td>
<td>Slurry crystallization</td>
<td>Synergistic effects and improved physicochemical properties reported</td>
<td>[90]</td>
</tr>
<tr>
<td>Ticagrelor–aspirin</td>
<td>Antithrombotic</td>
<td>Sonic and cooling crystallization</td>
<td>Tailor made for prevention of arterial thrombotic complications in patients with coronary artery, cerebrovascular, or peripheral vascular disease</td>
<td>[15]</td>
</tr>
<tr>
<td>Tramadol–paracetamol</td>
<td>Analgesic and NSAID</td>
<td>Solvent evaporation</td>
<td>Highly soluble with improved bioavailability, enhanced stability and synergistic actions</td>
<td>[86]</td>
</tr>
<tr>
<td>Tramadol–naproxen</td>
<td>Analgesic and NSAID</td>
<td>Slurry crystallization</td>
<td>Taste masked, highly soluble, with enhanced stability and synergistic actions</td>
<td>[87] [88]</td>
</tr>
</tbody>
</table>
the combined choice does not affect the stability of each compound. Similarly, incompatibility between the selected combinations of therapeutic agents could generate new impurities. Solubility would be one of the crucial factors to be addressed when dealing with a combination of two hydrophobic drugs, such as paclitaxel, rapamycin, imatinib, quercetin, curcumin, or resveratrol, both in terms of solvent selection for crystallization and to evaluate the impact on various pharmaceutical properties. Differential solubility could also be an issue, while exploring combinations with highly soluble drugs, such as piracetam, beta blockers, tramadol, and venlafaxine, could often lead to crystallization of the component units. Dose variability is also a big concern, given that most co-crystals are formed with a 1:1 stoichiometry. For example, exploring co-crystal formation between dihydropyridine classes of drug, such as amlodipine, with a dose of 2.5–10 mg, with a ‘sartan’ series, such as valsartan, with a dose range of 80–320 mg, would be difficult and is not preferable. To counter the disadvantages of such drugs, nutraceuticals with inherent therapeutic effects could be explored. Wider dose ranges and higher LD₅₀ values would make them ideal co-formers for MDCs compared with drug molecules. The quercetin–metformin combination [18] and mesalamine combinations with various amino acids and flavones [16] have shown synergistic activity in animal models. Quantification of unit components might be challenging when dealing with multiple drugs, especially nutraceuticals, which have poor solution-state stability.

Enhancements in the physicochemical properties for MDCs have been reported, but should be read with caution, given that some properties may show deterioration compared with individual drugs. Nakao et al. reported reduced dissolution rates of theophylline–phenobarbital MDC compared with pure forms of each drug [7]. Braga et al. reported reduced solubility of lithium salts upon co-crystallization with piracetam, whereas the IDRs of co-crystals were comparable to those of pure drug [14]. Surov et al. reported MDCs of diflunisal and theophylline with dissolution profiles similar to those of plain drugs [27]. Chattoraj et al. recently described deteriorated crystal plasticity and compaction properties in piroxicam–saccharin co-crystals [86]. Thus, the exploration of supramolecular interactions responsible for the physicochemical attributes of MDCs could help in designing computational methodologies that could predict material outcomes. Addressing current challenges and developing such prediction models would speed up the development of MDC-based commercial products.

Future perspectives
As described in the previous section, the selection of appropriate drug combination for development is challenging, with multiple factors to consider, including therapeutic applications, differential solubility, and drug–drug interactions. Yet, attempts could be made to choose relevant combinations from already available FDCs, to explore the possibilities of co-crystal formation, and to evaluate their potential benefits. Given the major hurdles involved in the development of drug–drug co-crystals, drug–nutraceuticals combination could be advantageous and relatively more easy to develop. Most nutraceuticals are weakly ionizing compounds that display poor bioavailability [87]. Numerous clinical trials are investigating the potential benefits of various nutraceuticals in multiple disorders, including Alzheimer’s disease, arthritis, cardiovascular disease, cancers, diabetes, obesity, macular degeneration, and osteoporosis [88,89]. Nutraceutical-based therapeutics, such as apigenin, berberine, baicalin, boswellic acid, capsaicin, carcinos acid, curcumin, ellagic acid, epigallocatechin gallate, genistein, glucosamine, hesperidin, kaempferol, lipioc acid, lutein, luteolin, naringenin, resveratrol, quercetin, pterostilbene, rosmarinic acid, silybin, tricin, thymoquinone, and wurninchin, could offer potential platforms for designing therapeutic hybrids along with drugs. Nutraceuticals with associated therapeutic effects, ease of availability, and robust supramolecular synthons (O-H, COOH, C=O, among others) could find applications as potential coformers for developing synergistic hybrids [18]. In a recent review, Sinha et al. discussed the potential for the co-crystallization of nutraceuticals [87]. The authors proposed the exploration of highly soluble drugs as coformers for the co-crystallization of nutraceuticals with bioavailability and stability issues to fortify their physicochemical and biopharmaceutical properties. This could lead to the emergence of an entirely new range of safer and effective therapeutic hybrids, a unique combination of pharmaceuticals and therapeutically effective nutraceuticals with synergistic benefits and reduced adverse effects [90].

Exploring the potential of inorganic systems to develop novel ionic co-crystals (ICC) could also offer new platforms for the development of therapeutic hybrids. ICCs are less explored and the literature available on pharmaceutical ICCs is limited. Lithium-based therapeutics have been well explored, along with the racemate class of drugs, for their application in the treatment of psychiatric disorders [14,91–94]. Exploring the potential of lithium and magnesium salts to form co-crystals with various drugs and nutraceuticals could provide new modalities for the treatment of various psychiatric disorders [95] and neuropathic pain [96], respectively.

Merging the principles of supramolecular design with nanotechnology could help in the synthesis of nano co-crystals (NCC). Of all the nanotechnology-based products, single-drug nanocrystals have been the most successful because of efficient productive capacities [97]. Limited literature is available on NCCs specific to pharmaceuticals. Sander et al. reported the first pharmaceutical NCC, caffeine–dihydroxy benzoic acid (DHBA), prepared by antisolvent crystallization using a sonochemical process [98]. Recent findings related to NCCs of caffeine with oxalic acid and glutaric acid published by Spitzer et al. gave new hope for the emergence of drug-based NCC products [99]. De Smet et al. successfully developed a NCC of itraconazole (ITZ) with carboxylic acids using wet milling. Developed formulations have shown faster release and lower Tₘₙₘᵢₐ in dogs compared with reference formulations [100]. By identifying robust synthons for co-crystal formation in anticancer therapeutics, such as S-FU, anastrozole, dasatinib, gefitinib, tamoxifen, mercaptopurine, 6-mercaptopurine, estramustine, cyclophosphamide, levamisole, capcetabine, and exemestane, one can easily foresee rapid growth in the development of NCC. Cancer and pain-related disorders could form a potential platform for the development of multidrug NCCs with enhanced bioavailability and fast dissolving capabilities to achieve faster onset of action.

Concluding remarks
Despite outstanding developments in the field of co-crystals, their commercial success is still awaited. There is a need for crystallographers, chemists, analysts, and pharmaceutical scientists
across the globe to collaborate, contribute, and move towards the development of robust models for predicting MDC formation, to give useful insights into the relevance of supramolecular interactions and their molecular outcomes, and to provide mechanistic understanding of the association and dissociation patterns of MDCs. Attempts are underway to quantitatively rank supramolecular synthons on the basis of energy differences [101,102]. Quantifying a supramolecular interaction and predicting the outcome to tailor physicochemical properties accordingly could bring a new era in crystal engineering, especially in the development of MDC-based therapeutic hybrids. Significant understanding of the drug-related mechanisms required to result in synergistic effects and reduce adverse effects would help to successfully develop marketable MDC products in near future. MDCs offer unlimited opportunities for development, including the exploration of new prediction models, designing scalable production processes, and the development of nanoscale co-crystals. Exploring co-crystallization on novel platforms, such as stents, sutures, or prostheses could result in revolutionary changes in implant-based therapeutic interventions, especially in the treatment of cardiovascular disorders. Inspecting the potential combinations of nutraceutical polyphenols and drugs that can be co-crystallized on such platforms would also open new avenues in the treatment of surgical site infections. With nanocrystal representing most of the successful nanotechnology-based products, one could foresee a bright future for NCC-based pharmaceutical products incorporating unit components with potential synergistic effects.

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