Reviews • POST SCREEN

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

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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 ethenzamide and gentisic 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 synthonic engineering, use of molecular descriptors, hydrogen-bonding propensity and pK_a-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 pK_a-based prediction depicts that a salt is formed if the difference between the pK_a base and pK_a acid (ΔpK_a) is >3, whereas a $\Delta pK_a < 0$ will generally result in the formation of a co-crystal [34]. By contrast, a ΔpK_a 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 $0 < \Delta pK_a < 2.5$ region as a salt/co-crystal continuum zone [39]. After studying 6465 crystalline complexes in the CSD, and validating and quantifying the ΔpK_a rule, Cruz Cabeza et al. recently reported a linear relation between ΔpK_a and the possibility of proton transfer between acid–base pairs. They concluded that $\Delta pK_a < -1$ would exclusively result in a non-ionized complex; $\Delta pK_a < 4$ would result in an ionized complex; and between $1 \leq \Delta pK_a \leq 4$, a 1 ΔpK_a difference would increase the probability of proton transfer by 17% from 10% at $\Delta pK_a = -1$ to 95% at $\Delta pK_a = 4$. Cruz Cabeza et al. concluded that ΔpK_a 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 1

Drug–drug and nutraceuticals co-crystals developed to date[a]

Drug combination	CCDC Ref code	Therapeutic category	Method of preparation	Observations	Refs
Theophylline–phenobarbital (2:1)	THOPBA	Antiasthmatic and sedative hypnotic	Distillation	Dissolution of theophylline and phenobarbital faster in pure powder than from co-crystal	[7]
Sulfadimidine–aspirin (1:1)	VUGMIT	Antibacterial and NSAID	Solvent evaporation	Pharmaceutical properties not evaluated	[28]
Sulfadimidine–4-ASA (1:1)	VUGMOZ	Antibacterial			[28]
Theophylline–5-FU (2:1)	ZAYLOA	Antiasthmatic and anticancer			[29]
Trimethoprim–sulfadimidine (1:1, 1:2)	RASSUZ	Antibacterial			[30,31]
Trimethoprim–sulfamethoxy pyridazine (1:1)	QUASHEX	Antibacterial	Heating at boiling point followed by instant cooling		[32]
Tetroxoprim–sulfametrole (1:1)	IRIMEB	Antibacterial	Cogrinding and solvent evaporation	Physical conditions essential for isolating two distinct polymorphic forms via desolvation were established	[33,34]
Piracetam–gentisic acid (1:1)	DAVPAS	Nootropic agent and NSAID	Co-grinding, slurrying in water and solvent evaporation	Role determined of carboxylic acid–primary amide dimer in crystal engineering involving two APIs that are polymorphic in nature	[35]
Amoxicillin trihydrate–potassium clavulanate (3:7, 5:5, 7:3)	–	Antibacterial and β-lactamase inhibitor	Melting at 50°C for 30 min	No significant improvement in activity observed	[36]
Lamivudine–zidovudine (1:1)	COWSOX	Antiviral	Solvent evaporation	Established synthon theory as a model for prediction of co-crystals from single compound	[37]
Theophylline–gentisic acid (1:1)	DUCROJ	Antiasthmatic and NSAID	Thermally assisted solvent evaporation	Pharmaceutical properties not evaluated	[38]
Ethenzamide–gentisic acid (1:1)	QULLUF	Both drugs are NSAIDs, latter also has anttaging properties	Solvent evaporation	Three polymorphic forms of ethenzamide and gentisic acid identified with twofold increase in IDR	[20]
Sulfamethazine–theophylline (2:1)	AWIJEW01	Antibacterial and antiasthmatic		Hygroscopicity of theophylline and sulfamethazine co-crystal decreased compared with controls	[24]
Meloxicam–aspirin (1:1)	ARIFOX	NSAIDs	Solution crystallization, slurry and solvent drop grinding methods	44-fold increase in pH 7.4 phosphate buffer solubility along with improved C_{max}, MRT, AUC, and MAT. Bioavailability improved fourfold	[21]
Isoniazid–4-ASA (1:1) Pyrazinamide–4-ASA (1:1)	URUDER URUGIY	Antitubercular drugs	Solvent drop grinding	Rare case of simultaneous existence of pure hydrogen-bonded and partially ionic carboxylic acid/nitrogen-based dimers observed within the same crystal structure	[39]
Carbamazepine–salicylic acid (1:1)	MOXWAY	Antiepileptic and anti-inflammatory	Unexpected in presence of moisture	Co-crystals formation mediated by water released by dibasic calcium phosphate dihydrate; detection of in situ co-crystal formation	[40]
Pyrazinamide–diflunisal (1:1)	–	Antitubercular and NSAID	Ball mill grinding	Density functional theory calculation used to study feasibility of co-crystal formation involving two APIs	[41]
Curcumin–pyrogallol (1:1)	AXOGIE	Anticancer	Liquid-assisted manual grinding	Dissolution rate 12 times faster than for curcumin alone	[22]
Aceclofenac–paracetamol (1:1)	–	NSAIDs	Various methods	Enhanced solubility of both drugs reported	[23]
Isoniazid–2-chloro-4-nitro benzoic acid (1:1)	LATLEZ	Antitubercular and antiviral compounds	Solvent evaporation	Pharmaceutical properties not evaluated	[42]
Piracetam–lithium chloride (1:1)	VEDDEP	Nootropic agent and mood-stabilizing agent	Solvent evaporation and grinding	Insignificant improvement in IDR reported	[14]

TABLE 1 (Continued)

Drug combination	CCDC Ref code	Therapeutic category	Method of preparation	Observations	Refs
Furosemide–pentoxifylline (1:1)	FEFYAS	Loop diuretic; the latter drug is used to treat intermittent claudication	Solvent evaporation	Pharmaceutical properties not evaluated	[43]
Pyrimethamine–carbamazepine (1:1)	KICWOK	Antimalarial and antiepileptic			[44]
Pyrimethamine–theophylline (1:1)	KICWIE	Antimalarial and antiasthmatic	Solvent evaporation		
Ciprofloxacin–norfloxacin (1:1)	KEXGAX	Antibacterial		Heteroassociation between fluoroquinolones reported for first time	[45]
Paracetamol–indomethacin and mefenamic acid (1:1)	–	NSAIDs		Pharmaceutical properties not evaluated	[46]
Sildenafil–aspirin (1:1)	DISXOU	Antihypertensive and NSAID		Enhanced intrinsic dissolution rate observed compared with marketed product	[26]
Diclofenac and Diflunisal–Theophylline (1:1)	–	Antiasthmatic and NSAID	Solvent drop grinding and solvent evaporation	Products showed enhanced stability and comparable dissolution rates	[27]
Dapsone–sulfanilamide flavone, luteolin, caffeine and benzothiazolone (1:1)	–	Antileprotic, antibacterial and antioxidants	Solution crystallization	Enhanced physical stability and increased solubility observed	[25]
Carbamazepine–ibuprofen	–	Antiepileptic and NSAID	Solution crystallization	Developed MDC using non-stoichiometric methods; pharmaceutical properties not evaluated	[47]

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

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].

MDC preparation begins with dry grinding followed by liquid-assisted grinding and slurry crystallization techniques for rapid screening. Solution crystallization methodologies require knowledge of the solubility of the unit components and are usually screened using ternary phase diagrams [52]. The success in forming a MDC by solution crystallization is determined by many factors, including the differential solubility of unit components, appropriate choice of solvent, final pH after dissolution of components, supersaturation, temperature, rates of evaporation or cooling, differential solubility, and presence of impurities. Thermal-based methods are also used in the screening of co-crystals [42]. Compounds with lower melting points are preferred for melt-based techniques. The degradation of unit components upon heating

and in the presence of a second component should be ascertained, and care should be taken to avoid such degradation during the developmental process. For further details on the preparation methods for single-drug co-crystals and how they can be applied for the synthesis of MDC, we refer the readers to previously published studies [50,51,53]. Developed co-crystals can then be successfully characterized using various analytical techniques and evaluated for various parameters (Fig. 2).

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
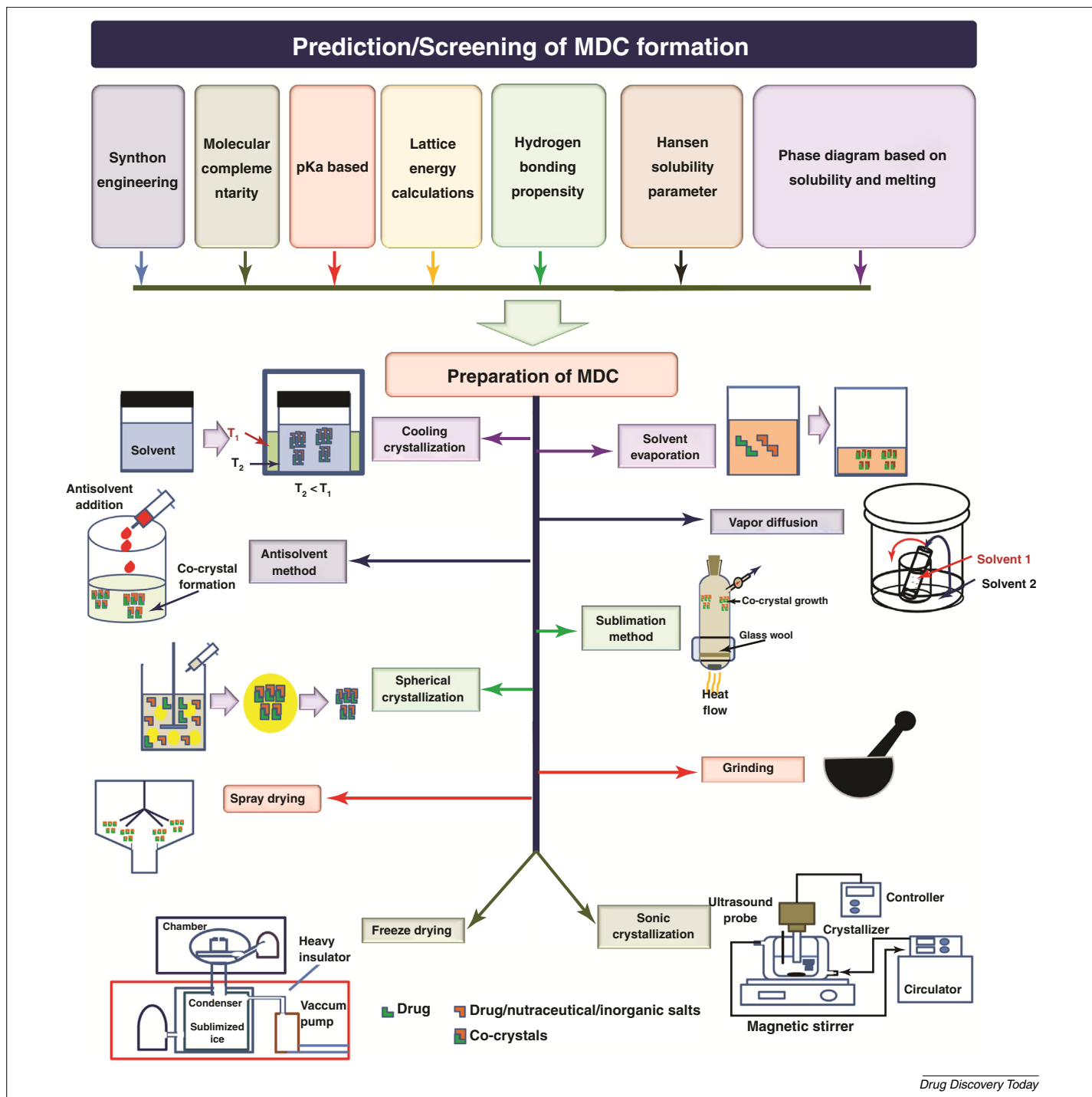
FIGURE 1

Pictorial representation of prediction/screening methods and preparation methods for synthesis of MDC.

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
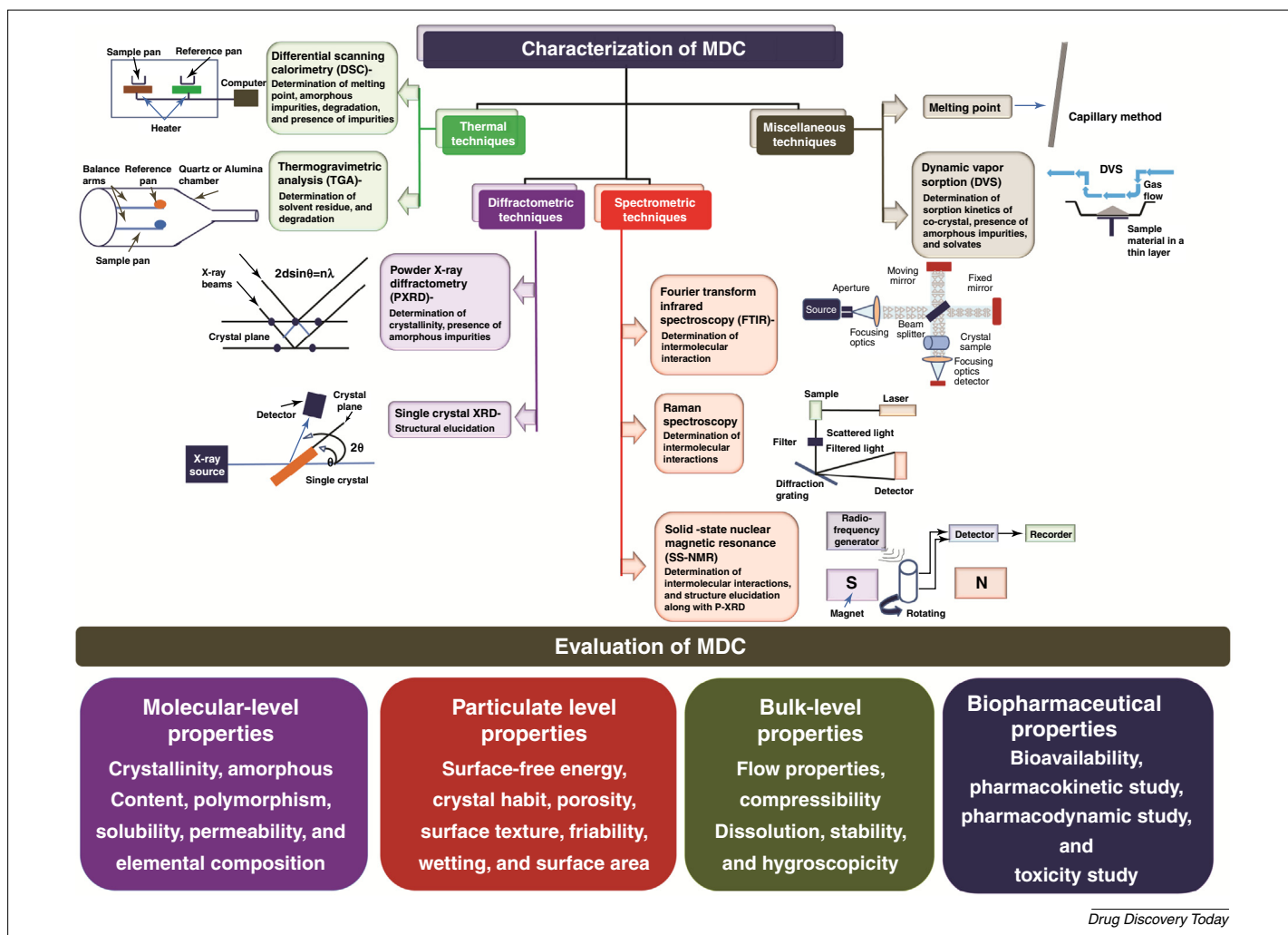
FIGURE 2

Overview of different characterization techniques available and evaluation of parameters available for MDC evaluation.

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

TABLE 2

List of patents available on MDC

Drug combination	Therapeutic category	Method of preparation	Remarks	Refs
ASA–theanine	NSAID and psychoactive	Grinding and rota evaporation	Water-soluble aspirin for intravenous formulations	[92]
Cyprodinil–dithianon	Fungicides	Various methods	Synergistic effects observed in biological experiments	[91]
Duloxetine–naproxen Venlafaxine–celecoxib	Antidepressant and NSAID Antidepressant and NSAID	Cooling crystallization Solvent evaporation and cogrinding	Improved solubility, IDR, and bioavailability, thereby increasing dose response; decreased hygroscopicity and enhanced stability also observed	[85] [89]
Ciprofloxacin and norfloxacin with various co-crystal formers	Antibacterial	Solvent drop grinding	Higher solubility, dissolution rates, and improved stability compared with parent compounds	[17]
Mesalamine with alpha amino acids, flavones, and nutraceuticals	Anti-inflammatory	Thermally assisted solvent evaporation and solvent drop grinding	Increased residence time and synergistic action reported	[16]
Metformin–oleoylethanolamide	Antidiabetic and antiobesity	Solvent drop grinding	Improved bioavailability with additional antiobesity action	[19]
Quercetin–metformin	Antioxidant and antidiabetic	Melting, solvent drop grinding	Improved solubility, IDR, stability, and great therapeutic potential obtained	[18]
Telmisartan–beta blockers	Antihypertensive	Slurry crystallization	Synergistic effects and improved physicochemical properties reported	[90]
Ticagrelor–aspirin	Antithrombotic	Sonic and cooling crystallization	Tailor made for prevention of arterial thrombotic complications in patients with coronary artery, cerebrovascular, or peripheral vascular disease	[15]
Tramadol–paracetamol	Analgesic and NSAID	Solvent evaporation	Highly soluble with improved bioavailability, enhanced stability and synergistic actions	[86]
Tramadol–naproxen Tramadol–celecoxib	Analgesic and NSAID Analgesic and NSAID	Slurry crystallization Cogrinding and seeding crystallization	Taste masked, highly soluble, with enhanced stability and synergistic actions	[87] [88]

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], ethenzamide–gentisic 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

the chosen combination 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 LD_{50} 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, baicalein, boswellic acid, capsaicin, carnosic acid, curcumin, ellagic acid, epigallocatechin gallate, genistein, glucosamine, hesperidin, kaempferol, lipoic acid, lutein, luteolin, naringenin, resveratrol, quercetin, pterostilbene, rosmarinic acid, silibinin, tricin, thymoquinone, and wurunchin, 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 racetam 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 anti-solvent 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 T_{max} in dogs compared with reference formulations [100]. By identifying robust synthons for co-crystal formation in anticancer therapeutics, such as 5-FU, anastrozole, dasatinib, gefitinib, tamoxifen, mercaptopurine, 6-mercaptopurine, estramustine, cyclophosphamide, levamisole, capecitabine, 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.

Acknowledgment

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