



Pharmaceutical cocrystals: from serendipity to design to application

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The field of pharmaceutical cocrystals has reached a tipping point, particularly because cocrystals can improve the physicochemical properties of drugs without compromising their therapeutic benefit. Accounts of cocrystal investigations in the literature started in earnest in 2003 and patent applications soon followed. The frequency of both has steadily accelerated, demonstrating an enhanced understanding of the design, characterisation, and manufacture of cocrystals and heightened interest from industry. Indeed, there were four new product approvals from 2014 to 2017 and more are in the pipeline. Here, we review all marketed drug products that are based upon pharmaceutical cocrystal drug substances, starting with the first recorded example, Beta-Chlor[®] in 1963, with a particular emphasis on their discovery, rationale for use, and market impact.

Introduction

Solid form optimisation: serendipity or design?

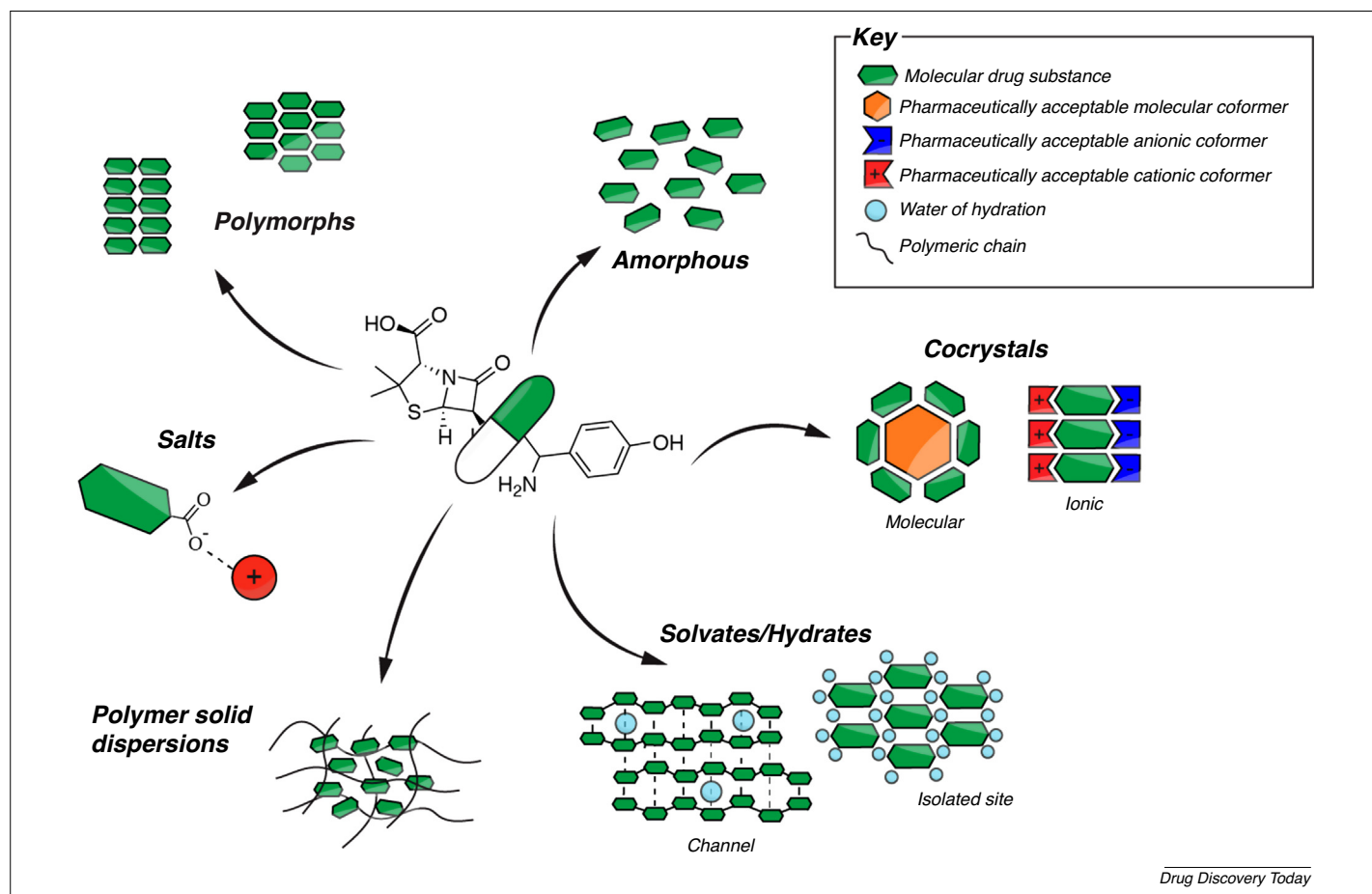
In 2013, Merck and Pfizer announced a joint collaborative effort to bring a promising new antidiabetic, Steglatro[®], to market [1]. They closed out 2017 by obtaining US Food and Drug Administration (FDA) approval with analysts predicting blockbuster status for their compound [2,3]. Steglatro[®], a molecular cocrystal of ertugliflozin and L-pyroglutamic acid, is the latest in a recent flurry of drug approvals made possible by crystal engineering principles developed during the early 2000s which include: Odomzo[®] (cocrystal of sonidegib and phosphoric acid), Suglat[®] (cocrystal of ipragliflozin and L-proline), and Entresto[®] (cocrystal of valsartan and sacubitril). The story of how academic curiosity and advances in X-ray diffraction enabled the field of crystal engineering to grow rapidly has been covered in detail in the literature [4,5]. Academic and industry researchers were quick to uncover the potential of the cocrystal approach to manipulate the physical properties of the solid state, particularly in an application area where the solid state is so valuable: pharmaceuticals [6,7]. This is

part of an aspect of preclinical research that has been termed ‘Molecules, Materials and Medicines’, or M³ [8].

It is no secret that many new chemical entities suffer from low solubility and/or poor permeability; up to 90% of new drugs receive BCS II classification [9]. This presents a major challenge for pharmaceutical science. If a drug cannot dissolve in the gastrointestinal tract (GIT) or penetrate tissues, then it will have difficulty finding therapeutic use. For decades, formulation scientists have been using solid form optimisation strategies, such as those summarised in Fig. 1 [10]. Each strategy brings its own advantages and disadvantages, each to be weighed against manufacturing challenges, regulatory risks, and the desired mode of action of the drug substance in question.

Cocrystals are ‘... solids that are crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts.’ [11]. Cocrystallisation in relation to pharmaceutical science is an area that has grown rapidly since several key publications in 2003–2004 demonstrated how crystal engineering can be applied to drug substances such as aspirin [7], ibuprofen [7], fluoxetine [12], carbamazepine [13], and itraconazole [14]. These landmark papers came about at least in part because the field of

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**FIGURE 1**

Summary of approaches to solid form optimisation.

crystal engineering [6] had progressed to the point where serendipity, exemplified by the discovery of the first cocrystal (urea and NaCl) in 1783 [15], had been replaced by crystal design principles. Figure 2 reveals the impact of these papers on the academic community, namely an almost exponential rise in publications on the topic of cocrystals after 2004, which has been mirrored by a similar trend in the frequency of patent applications relating to cocrystals. Although the term ‘cocrystal’ is also used in structural biology, search terms were used to minimise hits for these publications while minimising the omission of pharmaceutical cocrystals.

In this review, we explore how pharmaceutical cocrystals have emerged and present an overview of existing examples of intentional and nonintentional FDA-approved pharmaceutical cocrystal drug products. We also discuss how regulatory ambiguity initially made it difficult to advance the field, particularly in a risk-adverse industry, such as pharmaceuticals. Finally, we look ahead to the future of pharmaceutical drug products by examining pharmaceutical cocrystal products in the clinical pipeline and assessing the potential impact of cocrystals on current commonly prescribed drugs.

The cocrystal advantage

Regulatory green light

The pace and complexity of scientific innovation can make it difficult for public bodies to construct an appropriate regulatory frame-

work to maintain the fine balance between safety and allowing new technologies to thrive. Statutory instruments do not always get it right and, invariably, this maintains the *status quo*. Fenwick *et al.* provide an excellent analysis of this problem and highlight ways in which regulators can promote innovation (such as those used in the financial industry) so that ultimately the customer or patient can benefit from the latest innovative technology [16].

Unfortunately for the field of cocrystals, the *status quo* was maintained in February 2011, when the FDA published their draft guidance on the subject of cocrystals, defining them as ‘solids that are crystalline materials composed of two or more molecules in the same crystal lattice’. Here, they also considered cocrystals to be drug product intermediates (or in process materials) that are subject to additional manufacturing regulations under current good manufacturing practice requirements [17]. This made the risk-adverse pharmaceutical industry hesitant to spend research and development resources developing a troublesome solid form.

A seminal review paper that evolved from an Indo-US Bilateral Meeting explored the scientific debate regarding nomenclature of cocrystals and suggested that cocrystals should be classified with salts and how the FDA might approach reclassification of pharmaceutical solids [11]. Since then, further classification has been proposed [18]. Despite this paper and others like it (e.g., [19]), the FDA remained firm, releasing their full guidance document in 2013, which reinforced their previous perspective.

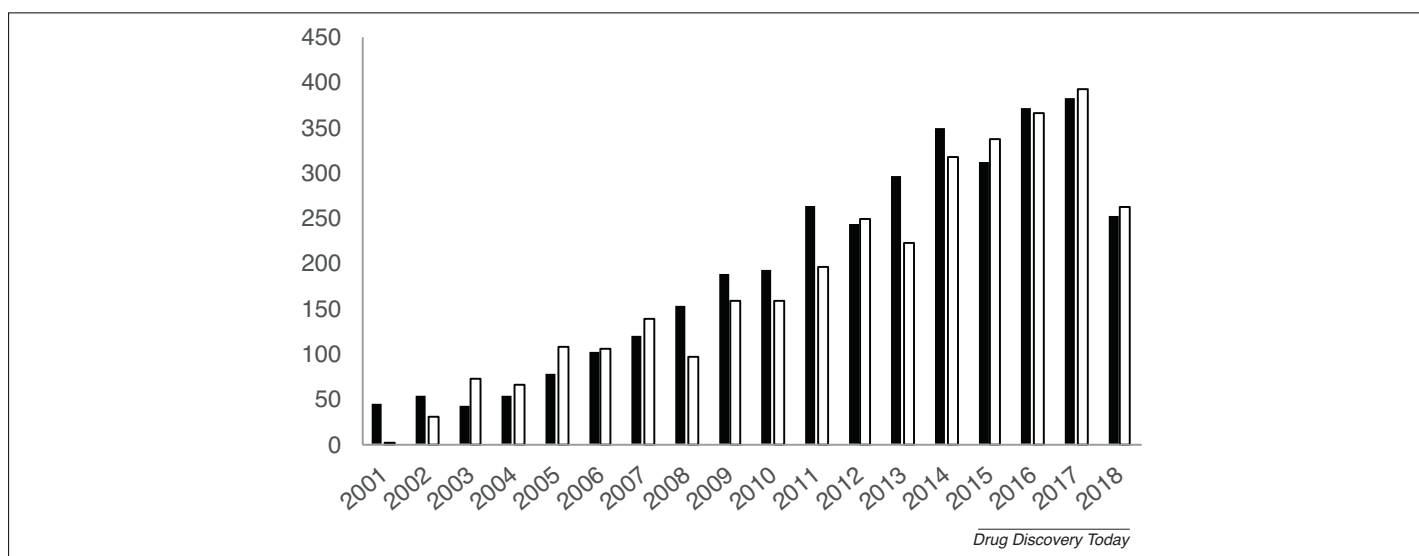


FIGURE 2

Cocrystal publications from 2001 to 2018 generated from a search of the Web of Science® database for terms 'cocrystal' OR 'co-crystal' NOT 'structural biology' NOT 'structural basis' (13 August 2018) (black bars) versus number of cocrystal patents from 2001 to 2018 generated from a search of the US Patent and Trademark Office Database for terms 'cocrystal' OR 'co-crystal' (10 August 2018) (white bars).

As a result, commercial interest in cocrystals waned, but has recently returned since the FDA modified their guidance in February 2016. This draft guidance classified cocrystals as active pharmaceutical ingredients (APIs), not drug product intermediates, and endorsed cocrystals as equivalent to polymorphs or salts of the API. This is potentially a significant development because it could enable both proprietary and generic companies to access the 505(b)(2) pathway for drug approval in the USA. The FDA released the final version of the Guidance in February 2018 [20].

FDA 505(b)(2) regulatory pathway

A key concept in the utilisation of cocrystals is that there is no change in the molecular structure of the medicine. This was recognised by the FDA in their recent guidance document in which they specifically state that 'cocrystals are considered the same as polymorphs or salts of the API from a regulatory perspective' [20], a welcome change from years previous. This could enable drug companies to seek FDA approval for their medicines using data from previous safety and efficacy investigations to bring a new product to market. Through 505(b)(2), companies can submit applications for medicines with new indications, substitutions of active ingredients, or (in the case of cocrystal applications) changes to the solid form [21]. In this way, the FDA has reduced the regulatory and financial burden to encourage innovation so that patients ultimately reap the benefits of the latest medicinal advances as soon as possible.

In Europe, the European Medicines Agency (EMA) released a reflective document in 2015 that classified cocrystals in a similar way to salts of the API [22]. Under their regulations, it means that the cocrystal is considered to be the same as the API unless it demonstrates different pharmacokinetic properties, an approach that industry considered more palatable. Today, a regulatory approval route similar to the 505(b)(2) is based on Article 10 of Directive 2001/83/EC where '... different salts, esters, ethers, isomers, mixture of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance

unless they differ significantly in properties with regard to safety and/or efficacy.' [22]

Intellectual property opportunities

Recent estimates put the cost of developing a new drug at US\$2.8 billion [23]. Furthermore, the number of approved drugs per billion of spending has halved each year since the 1950s. This ultimately drives up costs and puts further strain on global healthcare resources. Here, crystal engineering can offer a solution because new intellectual property (IP) opportunities exist for innovators who develop cocrystals of new and existing medicines, particularly if it results in improvement of pharmacokinetic characteristics of the API. This in turn may allow the drug to be used against different indications, enable manufacture, or improve purity of the final drug product [24]. Companies have begun to recognise the utility of cocrystals and this is evident by the addition of the phrase, 'the drug and any pharmaceutically acceptable cocrystals' to patents of new drug molecules [25]. There is also an opportunity for generic manufacturers to develop novel solid forms to overcome patent protection on existing marketed compounds.

Improved physicochemical properties

Although the diversity of possible crystal packing arrangements makes it difficult to predict the properties of a selected API and coformer upon crystallisation [26], Aakeröy *et al.* reported that coformers can be selected to systematically change the properties of solid forms. They demonstrated that increasing the carbon chain length of coformers leads to predictable decreases in solubility [27]. This concept could be applied to alter the pharmacokinetics of an API, which can result in drugs previously shelved finding their way into the clinic. Furthermore, because the cocrystal form may enable greater solubility and subsequent absorption of the API, one might find that less API is required in the dosage form, as is the case with Entresto® [28].

When a kinetically stable solid form is conferred by cocrystallisation, pharmacokinetics can exhibit what is known as the 'spring

and parachute' phenomenon [29]. The phrase was first coined by Guzmán *et al.* and reflects the situation whereby a higher energy form 'springs' drug solubility past its solubility limit and agents, such as surfactants, can be used to maintain this state (the parachute) [29]. The use of higher energy forms [30] and the importance of the supersaturation state [31] are not new concepts in pharmaceutical science, indeed, they were first documented by the Higuchi brothers during the 1960s [30,31] and are now applied in the field of cocrystals. Work is ongoing in this area to understand the mechanism of cocrystal solubility [32–34] and study the effects of endogenous conditions on this mechanism [35]. Other properties conferred by cocrystals include improved tabletability [36], reduced hygroscopicity [37] increased permeability [38], and controlling drug release rates [39], among others explored in several reviews [6,40,41].

Crystal engineering in pharmaceuticals

Crystal engineering is a term first coined by Pepinsky in 1955 [42] and implemented by Schmidt in 1971 [43]. Desiraju [5] and Etter [44] later identified, characterised, and utilised the supramolecular interactions to generate new solid forms [45]. Today, crystal engineering is a diverse field, as detailed in recent reviews [4,5]. In pharmaceutical science, the ability to rationally select coformers for a desired API is a cornerstone of the field [6]. This design approach is enabled by the discovery of pharmaceutically relevant supramolecular synthons, which are subsequently ranked by the propensity of formation to generate a synthon hierarchy [13,46–50]. Although not predictable 100% of the time, such understanding provides a reasonable expectation that crystal engineers can take any API and develop a cocrystallisation strategy.

There are two main classifications of cocrystals, ionic cocrystals (or charge assisted) and molecular cocrystals. There are important differences. First, molecular cocrystals generally comprise two components, a biologically active molecular compound and a pharmaceutical acceptable molecular coformer. Ionic cocrystals must have an additional variable because they comprise at least three moieties: an anion, a cation, and a neutral component, one of which is biologically active. This additional variable creates an exponentially larger array of possible compositions and increased likelihood of uncovering a solid form with desirable characteristics. Second, ionic cocrystals are sustained by charge-assisted supramolecular synthons, which are less likely to be impacted by solvent and more likely to afford large property variations [51].

Overcoming cocrystal disadvantages

Based upon the above, it can be asserted that cocrystals offer a low-risk, low-cost, but high reward route to new and better medicines. In essence, cocrystals offer a means to control the physiochemical properties of a medicine by addition of a suitable coformer. Coformers should be cheap, pharmaceutically acceptable, of low molecular weight, and have multiple API-binding sites with the ability to form strong intermolecular interactions. These are not necessarily big hurdles to overcome, but they cannot be ignored. Furthermore, although cocrystals are no longer different to a salt from a regulatory perspective, there is nervousness about large-scale cocrystal manufacture. There are also concerns that addition of a coformer will contribute to a higher mass of dosage form. This could become unmanageable for drugs such as paracetamol, metformin, or valproic acid, where the dose of the drug product is on the gram scale. However, this apparent disadvantage can be mini-

mised by use of coformers with multiple binding sites to create a solid form with a 3:1 or 2:1 stoichiometric drug:coformer ratio. Additionally, a strategy whereby the salt of the drug can be crystallised with the parent acid or base can also be used, as was the case with Epilim[®], which exists as a 3:1 cocrystal of sodium valproate and valproic acid [52].

Commercially available cocrystals

Serendipity has a role in almost all great scientific discoveries, from microwaves to superglue to penicillin to Teflon. Naturally, scientists are reluctant to announce that luck was involved in their latest discovery, but novelty can only be uncovered and exploited when supported by scientific understanding. The ability of scientists to apply the scientific method to a surprising result is what can make unexpected discoveries all the more remarkable. The pharmaceutical industry is no stranger to this concept, because it regularly uses a screening strategy designed to induce the propensity of serendipity [53]. Indeed, as we discuss herein, many of the compounds highlighted earlier owe much to serendipity from their discovery, clinical application, and subsequent solid form optimisation. Herein, we address examples of both serendipity and rational design.

Serendipitous discoveries

Chloral betaine, Beta-Chlor[®]

Some years have passed since chloral betaine was referred to as the 'modern morphine' in Stoker's *Dracula* [54], but its presence in the clinic today (although limited) is a testament to its success. Although the US patent described its preparation in 1962 as being designed to primarily mask the unpleasant taste of chloral [55], that it is indeed a cocrystal was only revealed in 2016 [56]. This investigation by the Zaworotko group revealed that chloral betaine exists as a charge-assisted diol-carboxylate heterodimer, with further Cl[−]⋯O interactions forming a tetramer. The cocrystal confers increased thermal stability over the pure drug substance, an advantage that was clearly unanticipated by the original patent inventors [56].

Chloral has a long history; it was the first synthetic sedative, having been synthesised in 1832. It took the curiosity of the German pharmacologist Liebreich to uncover its sedating properties and facilitate its widespread use (and abuse) thereafter [57]. Indeed, toxicological analysis revealed that it was part of the cocktail that resulted in the death of Marilyn Monroe [58]. Erroneously, it was thought to liberate chloroform *in vivo*, thereby explaining its sedative effects. Chloral is now known to be a prodrug of trichloroethanol, which exhibits its effects via action on GABA_A receptors [59]. Chloral gained notoriety as a key item in the toolkit of Mickey Finn, a bartender from Chicago who used its potent properties to sedate and rob his customers.

Valproate semisodium, Depakene[®]

The use of valproic acid as a carrier for organic compounds is well documented and it stocked the shelves of laboratories globally during the early 20th century [60]. Scientists of that time knew little of the power of this humble agent, and its subsequent impact on the treatment and prevention of seizures for millions of patients. It was discovered and subsequently approved for epilepsy in France in 1967. Although it was originally thought to be moderately useful, its full potential was realised in Germany,

where higher doses were prescribed from its introduction [60]. Today, it is sold in various forms under Depakene[®], Depakote[®], or Epilim[®], and the clinical literature makes a distinction between three forms of valproate: valproic acid (free acid), sodium valproate (salt), and semisodium valproate (cocrystal) [52]. There is no evidence to suggest that administration of any particular form effects clinical outcomes; thus, they are considered bioequivalent. The *British National Formulary* notes, 'Semisodium valproate comprises equimolar amounts of sodium valproate and valproic acid' and 'Convulex[®] has a 1:1 dose relationship with products containing sodium valproate . . . care is needed if switching or making changes'.

The cocrystal structure contains a 3:1 ratio of sodium valproate and valproic acid, which has a sodium oxygen cluster surrounded by the lipophilic tail of valproate [52]. Despite the existence of several forms of valproate, the cocrystal formulation demonstrates superior solid form properties, particularly by reducing the hygroscopicity found with sodium valproate and valproic acid [61,62]. Clinically, the cocrystal is the dominant solid form for tablet formulations [63].

Caffeine citrate, Cafcit[®]

Citrated caffeine, or caffeine citrate, is another cocrystal that has stood the test of time. The *British Pharmaceutical Codex 1907* suggested that caffeine citrate has higher stability than the pure alkaloid in concentrated solution [64], and it was known previously as a complex of caffeine and citric acid until its structural characterisation in 2007 [65]. X-ray diffraction analysis revealed that the cocrystal is sustained by O–H . . . N hydrogen bonds between carboxylic acid groups of citric acid and imidazole moieties of caffeine. Additional O–H . . . O hydrogen bonds create a ring-like motif with alternating molecules of caffeine and citric acid [65].

Caffeine exhibits its effect as an adenosine antagonist and this results in stimulation of the respiratory centre, leading to increased sensitivity to carbon dioxide, which in turn increases respiratory rate and oxygen consumption [66]. Although a certain fraction is converted to theophylline *in vivo* (a commonly prescribed bronchodilator), it is the preferred agent to treat infantile apnoea because of its minimal adverse-effect profile. Cafcit[®] is a favourite case study to highlight how overdoses can occur, particularly because the dose of caffeine is half that of caffeine citrate. The danger is compounded because of changes in neonatal pharmacokinetics that influence the half-life of caffeine from 3–4 days in newborn infants to 5 h after 9 months. This case highlights the need for crystallographers to engage with clinicians to ensure that understanding of cocrystal drug forms is appropriately incorporated into clinical curricula.

Escitalopram oxalate, Lexapro[®]

Escitalopram is the left-handed configuration of the popular antidepressant citalopram, a racemic mixture of the two stereoisomers. Escitalopram is marketed as a cocrystal containing the escitalopram oxalate salt and oxalic acid, whereas citalopram is approved as the hydrobromide salt. Lexapro[®] gained a lot of press because of controversies regarding the 'obviousness' of this new structural enantiomer [67]. Although the developers ultimately succeeded in demonstrating the novelty of their enantiomer, the discovery of a new, patentable cocrystal form of this drug [68] was likely a heart sink moment for executives at Forest and Ludbeck laboratories. This synthon contains the escitalopram cation forming a salt by

way of two hydrogen bonds to the same oxalate dianion [N⁺–H . . . (O[–], O[–])]; this unit is linked into chains by a neutral oxalic acid molecule [68].

Recently, a ground-breaking network meta-analysis published in *The Lancet* concluded that escitalopram, agomelatine, and vortioxetine are the most effective and tolerable antidepressants available [69]. These results could influence current clinical practice, but some remain sceptical [70].

Sonidegib diphosphate, Odomzo[®]

Novartis discovered sonidegib, the second FDA-approved inhibitor of smoothened, a transmembrane protein involved in the Hedgehog pathway that is responsible for the transcription of several glioma-associated oncogenes [71]. Using rational drug design and computational analysis to screen over 10 000 compounds, the company subsequently refined its selection using structure–activity relationships to generate the lead compound [72].

Although monophosphate cocrystals with phosphoric acid have been designed previously [73], there is no published evidence that Odomzo[®] is a cocrystal by design. However, there is evidence to the contrary; the FDA chemistry review contains a reviewer comment that notes, with brevity, 'API is not a salt' [74]. In addition, the original patent application refers to mono- and diphosphate salts of the API [75]. Furthermore, an EMA assessment states that, although prepared as a cocrystal, it can breakdown on contact with water and they noted that this does not change absorption [76]. From this, one can conclude that it is unlikely that the sonidegib diphosphate cocrystal was created by design, notwithstanding the manufacturing problems it produced [76].

The EMA document states that this structure is known and that it contains the salt of sonidegib with phosphate, with another phosphate free acid to make a diphosphate cocrystal [76]. Although patent literature does not reveal the precise crystal structure, it does refer to several other cocrystals [77].

Crystal engineering of pharmaceutical cocrystals

Ipragliflozin L-proline, Suglat[®]

Suglat[®] represents a purposeful step of 'Big Pharma' into the cocrystal field; coincidentally, it is also the first approved sodium glucose co-transporter 2 (SGLT2) inhibitor in Japan. It was developed by Astellas and Kotobuki pharmaceuticals and was approved for use in Japan in 2014. Since its release, Astellas has recorded a year-on-year increase in sales, currently standing at ¥9.5 billion for the 2016 financial year [78]. Even in the face of fierce competition from dapagliflozin, canagliflozin, empagliflozin, among others, this product remains dominant, with 30% share of the Japanese market [78].

The team at Astellas and Kotobuki have described their steps towards discovery of the active moiety [79]. They opted for a crystal engineering approach because the parent compound form can switch reversibly from an anhydrous form to a nonstoichiometric hydrate depending on the storage conditions. The cocrystal form (ipragliflozin . . . L-proline) has consistent quality, does not absorb moisture, and was suitable to be brought forward into the drug product [80]. Suglat[®] is one of several success stories involving SGLT2 inhibitors, the role of which in diabetes pharmacotherapy is discussed in a pharmacological review by Gallo *et al.*, who noted that the results of ongoing long-term studies will determine the future of this therapy [81].

Valsartan/Sacubitril, Entresto®

The first multidrug cocrystal and the second case of cocrystal innovation from Novartis, Entresto® is a multidrug formulation that combines the angiotensin receptor inhibitor valsartan with a neprilysin inhibitor prodrug, sacubitril. Entresto® is a classic example of how cocrystals can influence pharmacokinetics. This formulation improves the bioavailability of valsartan, with a lower dose required to achieve the same therapeutic effect [28].

Although it contains valsartan, a drug approved by Novartis in 2002 [82], it is this addition of the first-in-class neprilysin inhibitor that sets this drug apart. Clinicians might be hesitant to prescribe Entresto® after the National Institute of Health and Clinical Excellence published an analysis of the much-publicised PARADIGM-HF trial [83], coupled with the significant cost differential between Entresto® (€1807) and other treatment options, such as valsartan (€109) or ramipril (€51) [28]. Despite this, Novartis reported profits of US\$507 m in 2017, and recent reports suggest it could reach revenues of US\$4–5 billion per year [84]. The formation of the large complex structure illustrates how unpredictable crystal structures can be, with the unit cell containing six sacubitril and six valsartan anions, 18 penta- and hexa-coordinated sodium cations, along with 15 water molecules [85].

Ertugliflozin L-pyroglutamic acid, Steglatro®

The second SGLT2 inhibitor as a cocrystal form was approved in 2017, emerging from Pfizer and Merck's collaborative efforts in previous years [1]. Similar to Odomzo®, this compound was generated by rational design using computational and high-throughput screening [86] and was ultimately selected because a suitable crystalline form of ertugliflozin itself was not found and it was not ionisable at physiological pH. Therefore, the team at Pfizer decided to pursue a cocrystallisation strategy [86]. Patent literature reveals that they uncovered three cocrystal forms of ertugliflozin: a 1:1 cocrystal with L-pyroglutamic acid (the marketed form) and 1:1 and 1:2 cocrystals with L-proline [87]. This is the second case for drugs within the SGLT2 class in which cocrystallisation was exploited to create a solid form suitable for manufacture and subsequent clinical application. Steglatro® was approved alongside Steglujan® [2], a fixed-dose combination containing ertugliflozin and sitagliptin, which demonstrates the robustness of the cocrystal form and the diversity of applications it can take (Table 1).

Pharmaceutically approved complexes suspected to be cocrystals

There are numerous examples within the scientific literature of drugs identified as 'complexes', although their exact structural

characteristics are yet to be determined. Indeed, it was only in 2016 that the crystallographic structure of chloral betaine was uncovered after 100 years of clinical use [56]. This prompted a search of the PubChem database using the terms 'complex' AND 'molecular complex' and manual searches of the *British Pharmaceutical Codex 1907* and *British National Formulary 74*. We thereby identified several potential pharmaceutical cocrystals through this approach (Table 2), but suspect there might be others.

Interestingly, *King's American Dispensatory 1898* described how some of these complexes can be generated. For example, caffeine citrate is prepared as follows, 'dissolve the citric acid in the hot distilled water, add the caffeine, and evaporate the resulting solution, on a water bath, to dryness, constantly stirring towards the end of the operation' [88]. Those in the field of cocrystallisation will notice the similarities here to the slurring approach that has been used for cocrystal discovery and scale-up [89]. It appears that, if one looks through old pharmacy texts, one might find robust methodologies to create cocrystals of the above for further characterisation. This list, and potential additions to it, provides scope for crystallographers to investigate the nature of these complexes; perhaps with a little luck there are interesting crystal engineering insights yet to be uncovered.

The future of cocrystals

Recent developments suggest that the field of pharmaceutical cocrystals has many fruits to bear, not least in finding new crystal forms, and the potential IP that might accompany such discoveries. There is also a developing understanding of how cocrystals behave in physiological environments and particularly how cocrystallisation could be applied to alternative routes of delivery. We also note that tentative steps have been taken by the pharmaceutical industry in the field of cocrystallisation, but there are still outstanding challenges, particularly with regards to continuous manufacturing. A recent review discusses how emerging process analytical technologies and continuous processing techniques can be applied to cocrystallisation [89].

Clinical trials

ClinicalTrialsRegister.eu and ClinicalTrials.gov were searched using the terms, 'Cocrystal' OR 'Co-crystal' and the results were compiled into Table 3.

Cocrystals of commonly prescribed drugs

The burst of literature activity since 2003 has resulted in an eclectic mix of cocrystals using pharmaceutically relevant compounds. A search of the Cambridge Structural Database

TABLE 1

Summary of commercially available pharmaceutical cocrystals

Drug	Date of FDA approval	Components	Indication
Beta-Chlor®	1963	Chloral hydrate ··· betaine	Sedation
Depakote®	1983	Valproic acid ··· [valproate sodium]	Epilepsy
Cafcit®	1999	Caffeine ··· [citric acid]	Infantile apnoea
Lexapro®	2002	[Escitalopram oxalate] ··· Oxalic acid	Depression
Suglat®	2014	lpragliflozin ··· L-proline	Diabetes
Entresto®	2015	[Valsartan sodium] ··· [sacubitril sodium]	Heart failure
Odomzo®	2015	[Sonidegib monophosphate] ··· phosphoric acid	Basal cell carcinoma
Steglatro®	2017	Ertugliflozin ··· L-pyroglutamic acid	Diabetes

TABLE 2

Summary of potential pharmaceutical cocrystals^a

Drug	Components	Indication	Source
Dichloralphenazone	Antipyrine, chloral hydrate (1:2)	Migraine	PubChem CID 10188
Iron sorbitex	Iron, sorbitol, sodium citrate (1:1:1)	Iron deficiency anaemia	PubChem CID 20715017
Nicotinamide–ascorbic acid	Nicotinamide, ascorbic acid (1:1)	Vitamin complexes	PubChem CID 54710212
Tetracycline phosphate	Tetracycline, phosphoric acid (1:1)	Broad-spectrum antibiotic	PubChem CID 54713149
Caffeine–sodium benzoate	Caffeine, sodium benzoate (1:1)	Headache	<i>British Pharmaceutical Codex 1907</i>
Caffeine–sodium salicylate	Caffeine, sodium salicylate (1:1)	Headache	<i>British Pharmaceutical Codex 1907</i>
Acridine–sulfonamide	Acridine, sulfonamide (1:1)	Antiseptic	PubChem CID 54710212

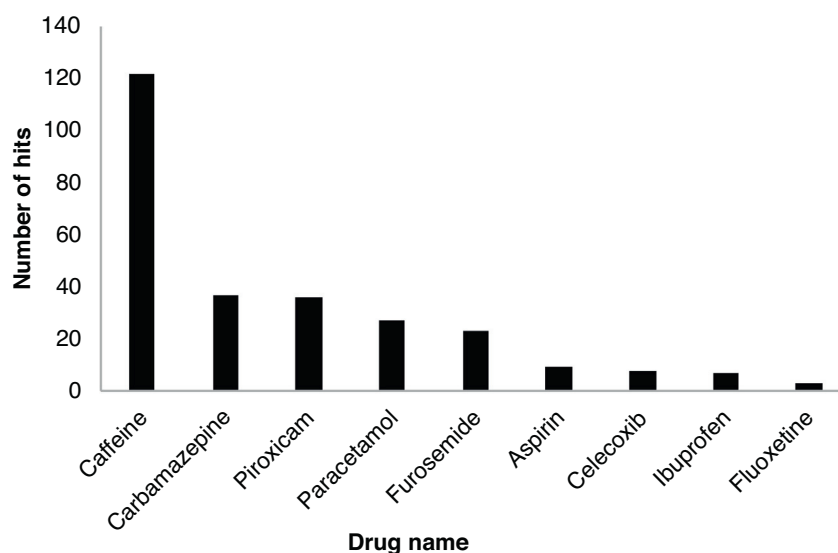
^a Compounds were identified as pharmaceutically approved 'complexes' from manual searches of PubChem database using the terms 'complex' AND 'molecular complex' and of the *British Pharmaceutical Codex 1907* and *British National Formulary 76*.

TABLE 3

Summary of cocrystal products currently in clinical trials^a

Drug	Phase	Company	Clinical trial identifier
TAK-020 (TAK-020–gentisic acid)	Phase I	Takeda Pharmaceuticals	NCT02723201
E-58425 (tramadol hydrochloride–celecoxib)	Phase III	Esteve	NCT03108482
CC-31244 (non-nucleoside polymerase inhibitor)	Phase IIa	Cocrystal Pharma	NCT0276075
T121E01F/T121E02F (zoledronic acid cocrystal)	'Phase III ready'	Thar Pharmaceuticals	NCT01721993

^a Compounds were identified from searches of ClinicalTrialsRegister.eu and ClinicalTrials.gov using the terms 'Cocrystal' OR 'Co-crystal'.



Drug Discovery Today

FIGURE 3

Selection of commonly prescribed drugs contained within the *British National Formulary 76* and number of cocrystal forms found on the Cambridge Structural Database (July 2018).

was conducted using ConQuest (v1.2.2, 2018) to determine the number of cocrystal forms of drugs that are commonly prescribed in the UK and Ireland. Figure 3 displays the results and, evidently, some compounds generate greater interest than others. Unsurprisingly, paracetamol, aspirin, and caffeine are among those with the greatest research activity, perhaps because of their ubiquity in academic labs as opposed to crystal novelties. It is clear that there is much scope for cocrystal research, and the benefits here are not just limited to trouble-

some compounds, because they can improve the utility of even the most widely prescribed medicines.

A comprehensive review in 2009 [41], followed by others in 2013 [90] and 2016 [6], illustrated the diversity of solid form changes that can occur upon cocrystallisation and reinforced how crystal engineering principles can create more desirable solid forms for use in pharmaceutical development. The numerous advantages brought by cocrystallisation can be compounded by the inclusion of a second API, as seen with Entresto[®] [24]. Here, paracetamol–indomethacin,

sildenafil–aspirin, or piracetam–lithium all show promise from a chemical and clinical perspective [91].

Concluding remarks

The road is clear for cocrystals to become an integral, accepted, and, possibly, preferred part of solid form screening for the materials side of drug development. Some early examples of commercial cocrystals might have been serendipitous but advances in crystal engineering have enabled their design by crystal engineering. Concurrent advances in technology have enabled rapid and accurate structural characterisation of novel cocrystals. Regulations, skills, and history are all in hand; now it is time to capitalise. Market routes, including regulatory approval, have been recently demonstrated for the aforementioned pharmaceutical cocrystals and market performance is more than encouraging. Furthermore,

there is opportunity for the development of bioequivalent cocrystals for use in generic products. Therefore, there is every reason to expect an increase in the number of approved pharmaceutical cocrystal drug products in the coming years. However, there remain challenges regarding rational selection of cofomer libraries, optimised screening methods, scaled-up manufacturing routes, and the impact of a cocrystal formulation on the dosage mass. We could now be beginning to enter an era of pharmaceutical cocrystal dominance: watch this space!

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