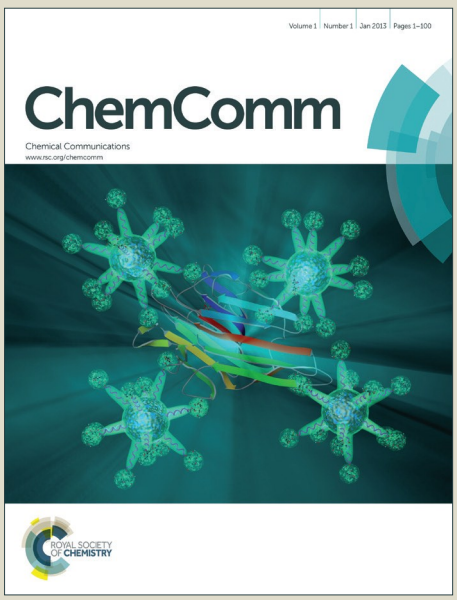
# ChemComm

Accepted Manuscript





ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

ARTICLE

# Engineering and manufacturing of pharmaceutical co-crystals: A review on solvent-free manufacturing technologies

S. A. Ross,[a] D. A. Lamprou[bc*] and D. Douroumis[a*]

Received 00th February 2016,
Accepted 00th May 2016

DOI: 10.1039/x0xx00000x
www.rsc.org/

**Design and synthesis of pharmaceutical cocrystals have received great interest in the recent years. Cocrystallization of drug substances offer a tremendous opportunity for the development of new drug products with superior physical and pharmacological properties such as solubility, stability, hydroscopicity, dissolution rates and bioavailability. It is now possible to engineer and develop cocrystals via 'green chemistry' and environmental friendly approaches such as solid-state synthesis in the absence of organic solvents. In addition, significant efforts are placed on computational screening, cocrystal manufacturing in a continuous manner and real-time monitoring for quality purposes by using various analytical tools. Pharmaceutical cocrystals are not fully exploited yet and there is a lot of ground to cover before they can be successfully utilized as medical products.**

## Introduction

Though the term cocrystal did not exist at the time, the first known to be created was reported in 1844 by the German chemist *Friedrich Wöhler* [1]; where formed a cocrystal of Quinone and Hydroquinone. Several other cocrystals were reported over the next century, however the phrase was first coined by *M.T. Etter* et al [2, 3] in 1992. Throughout the 1900s, numerus cocrystals have been discovered and as knowledge of intermolecular interactions has increased, it is possible to design cocrystals to achieve the desired physicochemical and biological properties of an Active Pharmaceutical Ingredients (API). The last decade has seen a renewed interest in cocrystals research, mostly due to increased interest in the pharmaceutical industry, due to the potential to enhance the physiochemical properties of known API which can be potentially patented and developed into a new marketable drug [3-5].

There is currently some debate as to the definition of a cocrystal. Most publications agree that a cocrystal is a crystalline structure, comprised of at least two components [6-8]. Under the US Food and Drug Administration (FDA) latest guidelines, cocrystals are defined as "Crystalline materials composed of two or more molecules within the same crystal lattice" [9]. However, a number of publications argued to use a more restrictive definition where the components are solid in their pure forms under ambient conditions and where these components co-exist as a stoichiometric ratio of a target molecule and a neutral molecule or coformer [10, 11]. However, others have argued that the restriction based on the ambient conditions is arbitrary [8]. A recent perspective[12], authored by 46 scientists aimed to come to a consensus on the exact definition of a cocrystal. The perspective states that: *'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'* [12]. It is important to note that a cocrystal is different in definition from a pharmaceutical cocrystal; the difference being that in a pharmaceutical cocrystal one of the components is an API and the other a coformer [13]. Because cocrystals are formed with their molecular components in a stoichiometric ratio the intermolecular reactions between the API and the coformer interact via non-covalent, such as ionic interactions, hydrogen bonding and Van der Waals interactions taken place [14].

Cocrystals are bi-molecular entities, which allow the formation of diverse crystal forms when compared to the component molecules. The diverse crystal structures, which stem from the intermolecular interactions of the cocrystal, enhanced the physical and chemical performance of the API which are far different from that of the individual compound. However, the key advantage that cocrystals hold is that while the API will benefit from physiochemical enhancements, the pharmacological properties will not be altered. The result is a largely bioavailable product [15]. The effect on the physiochemical properties of the API is dependent on the available coformer. With this in mind, it is possible to maximise an APIs bioavailability by careful selection of the coformer. This is necessary to achieve the drugs intended properties and to avoid any potential toxic effects, so a thorough screening process is needed to select the right coformer [16, 17]. It is important that the coformer is no known to have any toxic effects, or for that matter, any adverse effects which could affect the properties of the API. For example, it has been shown that using benzoic acid has the potential to increase the solubility of AMG 517 when they are cocrystallized, but that does not mean it is the case for all APIs [18]. For example, when

[a] *Faculty of Engineering and Science, University of Greenwich, Medway Campus, Chatham Maritime, Kent ME4 4TB, United Kingdom*
[b] *Strathclyde Institute of Pharmacy and Biomedical Science (SIPBS)s, University of Strathclyde, 161 Cathedral Street, Glasgow G4 0RE, United Kingdom*
[c] *EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC), University of Strathclyde, Technology and Innovation Centre, 99 George Street, Glasgow, G1 1 RD, United Kingdom*
** Corresponding authors: d.douroumis@gre.ac.uk, dimitrios.lamprou@strath.ac.uk*
*† Footnotes relating to the title and/or authors should appear here.*
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

benzoic acid is used as a coformer with fluoxetine hydrochloride, the opposite occurs and a decrease in solubility will be observed [19]. To prevent cocrystallizing with a coformer which has the potential to cause toxic effects, the coformer should be included on the US FDA 'Everything Added to Food in the United States' (EAFUS) list. This list comprises over 3000 substances that are suitable as food additives, or approved as generally regarded as safe (GRAS) [20]. Factors effecting the physiochemical properties of the cocrystal are the synthetic procedure employed, the properties of the API and coformer and the nature of the molecular interactions between the two. These parameters can be modified to improve the drug's properties. These properties include the solubility, dissolution, chemical stability, compressibility, hygroscopicity and melting point [21]. These factors all differ based on the API-coformer pairing and the nature of their interactions.

## Cocrystal properties

Due to the differences in molecular structure and the nature of the interaction between API and coformer, cocrystals will display different physiochemical properties. The cocrystals melting point is a prime example of how the selection of a coformer can engineer a drug with desirable properties. Studies have shown that is possible to raise or lower the melting point of API by selecting a coformer with a melting point greater or lesser of that of the APIs, for example, *Stanton and Bak* [18] investigated ten 1:1 cocrystals of AMG 517 with different coformers. The cocrystals all displayed a melting point between the API and coformer. They determined a correlation coefficient of 0.7849, which means 78 % of the variability of the cocrystals melting point, corresponds with the variability of the coformers' melting point. This suggests it is possible to tune the melting point of the cocrystal through the selection of coformer. For example, if one wanted to synthesize a higher melting cocrystal, then a higher melting cocrystal should be selected and vice versa if a cocrystal with a lower melting point is required [21]. The melting point is important during drug design and the fact it can be modified is makes cocrystals attractive to the pharmaceutical industry. It has been shown that there is a correlation between solubility and melting point and that a higher melting point demonstrates the new material is thermodynamically stable [22]. Lowering the melting point of cocrystals can also prove beneficial during pharmaceutical processing. For example, when dealing with heat-labile drugs such as carbamazepine, processing at high temperatures can cause chemical degradation [23]. In a 2011 report *Rahman et al.,* [24] selected Nicotinamide as a coformer for carbamazepine and was able to process solid dispersions at 160 °C using hot-melt extrusion (HME). This was far below the 190 °C melting point of the API, demonstrating it is possible to lower the melting point of carbamazepine through cocrystallization of a coformer with a much lower melting point (126 °C).

It is possible to enhance the chemical stability of an API through cocrystallization. For example, carbamazepine has been shown to undergo chemical degradation after forming a hydrate [25]. After cocrystallization with a saccharin coformer, the packing arrangement in the carbamazepine molecules is altered. As a result, the carbamazepine-saccharin cocrystals demonstrated favourable stability when compared to the bulk substance [26].

If a drug has a high hygroscopicity, it is likely that moisture uptake from the atmosphere will convert the drug into its hydrate form, leading to it displaying unwanted properties. Hydrate formation is dependent on the interactions between the API and the solvent in the crystals. Through cocrystallization it is possible to replace these API-solvent interactions. The reduced availability of unreacted hydrogen bonds inhibits hydrate formation in the crystalline lattice of cocrystals. This has been demonstrated in studies by *Trask et al* [27] where oxalic acid was employed as a coformer for caffeine and theophylline to produce cocrystals. Both cocrystals showed no signs of hydrate formation over a period of 7 weeks at 98 % relative humidity (RH) [28].

Due to the unique layer structure of cocrystals they have been shown to exhibit improved mechanical properties compared to the bulk product. This is of specific interest to the pharmaceutical manufacturing industry as to improve efficiency; pharmaceutical products must have specific compaction properties. *Sun and Hou* found that caffeine-methyl gallate cocrystals display good plasticity and improved tabletability, without lamination at high compaction force [29]. It has been found that by using nicotinamide as a coformer for ibuprofen and flurbiprofen, the resulting cocrystals display improved compressibility and improved tableting behaviour [30].

The past two decades has seen a substantial increase in the complexity and specificity of pharmaceutical drugs. The increased complexity has been accompanied by a decrease in the bioavailability of the API [28]. For a drug to be effective it must be readily available at the target site after administration, as bioavailability describes the degree to which a drug can achieve this. Solubility, permeability and stability are key factors which affect the bioavailability of pharmaceutical products. Approximately 40 to 70 % of drugs screened in industrial research have poor water solubility [31]. After delivery, pharmaceutical drugs must dissolve in the intestinal fluid in order to be absorbed into circulation. Poor solubility will limit the amount of API that is available for absorption. If the product also has poor permeability, then a further decreased amount of API will be able to transfer across the human intestinal membrane. Because of this the solubility and dissolution of the API is a major concern and one of the main challenges to overcome during drug development. The solubility must be enhanced whilst maintaining a stable form. This objective can be achieved through cocrystallization, which is part of the reason it has seen increased interest over the last decade [12, 32].

Drugs solubility is determined by the solvation of the components and the strength of the crystal lattice. To enhance drug molecules solubility, the solvent affinity must be increased and/or can lower the lattice energy. Both of these conditions can be met through cocrystallization [32]. Arguably the most important parameter which influences solubility and/or dissolution is the solubility of the coformer, which is the reason that the selection of the coformer is of paramount importance when designing drug formulations. Cocrystal solubility strongly correlates with the solubility of its coformer [33-35]. This is due to a decrease in the solvation barrier for a cocrystal to an extent which is proportional to that of the pure coformer. Other factors such as particle size, dissolution media, and cocrystal morphology have a reduced influence in cocrystal solubility [16].

In a 2009 study *Good and Rodriguez-Hornedo* [33], set out to establish the influence of the API and coformer on the cocrystals properties using carbamazepine, caffeine and theophylline and a selection of different coformers in order to test the solubility of a large number of cocrystals. The results proved that cocrystal solubility increases with the solubility of both constituents. The research suggests that selecting a coformer with a solubility 10-fold higher than the API will result in a cocrystal with enhanced solubility [33]. Though it is the strength of the lattice (which is primarily influenced by the coformer selected) which dictates solubility where there is little resistance to solvation. It has been shown that the dissolution media plays a great role in the cocrystals overall solubility. Solvation has been shown to dictate the aqueous solubility of the cocrystal, which is the reason of the selection of coformer it should ideally be one that's able to dissolve in conditions similar to the human gastrointestinal tract as to aid the drugs bioavailability. This demonstrates that decreasing the solvation barrier is the key to increasing cocrystal solubility [36, 37].

A recent study conducted by *Serrano et al* [38] demonstrated how the cocrystals morphology can determine the properties they exhibit. Four different cocrystals structures were formulated with their morphology confirmed through scanning electron microscopy (SEM); were either large plate-like, large prismatic, small cube-like or microsphere cocrystals. It was found that the microsphere cocrystals produced by spray drying resulted in much improved compaction properties and small cube like cocrystals demonstrated the faster dissolution.

## Importance in industry

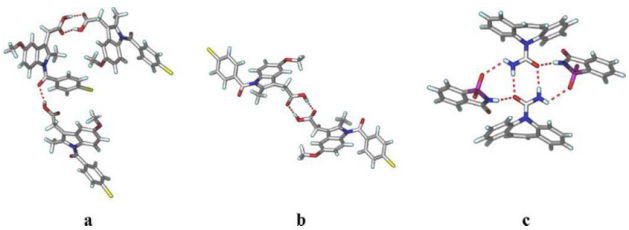
Though cocrystals have been long since discovered, cocrystallization has been a relatively un-researched area until recently. Cocrystal research is experiencing ever increasing interest due to their new found relevance in the pharmaceutical industry. This is mostly due to the fact they present opportunities to edit the composition of matter and change the chemical and or physical properties of molecules, without the need for covalent modification of the drug molecule [39]. As previously mentioned, cocrystals ability to enhance bioavailability and other properties give them a distinct advantage and for that reason the pharmaceutical industry has great incentive to research and develop cocrystals. As scientific understanding of the non-covalent mechanisms which dictate cocrystal properties has advanced, researched has increased.

This is not however the only reason scientific interest in cocrystals has increased. Because pharmaceutical cocrystals are structurally different to their bulk forms, it is possible to patent cocrystals of existing APIs as a new crystal form. In 1995 *Eli –Lilly* [40] patented complexes of cephalosporins and carbacephalosporins with parabens and various compounds and a cocrystal of sildenafil citrate and acetyl salicylic acid with higher solubility in acidic media was patented in 2007. If the cocrystal is then found to exhibit enhanced clinical advantages, the company can develop the cocrystal as a new drug [41, 42]. Cocrystals also have the potential advantage of shortening the drug development timeline. As the drug development groups are working with known API, much will already be known in the areas pertaining to drug discovery and toxicology [43]. Shorter development times equate to less cost, which is appealing to pharmaceutical companies. Cocrystals solid-state synthesis techniques can be classified as green chemistry as they offer high yield, no solvent use and there are few by-products. The continuous mechanisms used to form cocrystals also require low energy costs, which is attractive to pharmaceutical companies [44, 45]. However, marketed cocrystals products are expected to show a moderate growth due to the significant experimental efforts and regulatory risks related to their approval. In addition, the current industrial perspective considers cocrystals as an alternative for "difficult APIs" that is hard to crystallize or purify [46]. A typical example of marketed pharmaceutical cocrystals is sildenafil citrate known as Viagra (Pfizer) used to treat male erectile dysfunction and pulmonary arterial hypertension [47].

## Crystal engineering and Coformer selection

Crystal engineering is the construction of crystalline solid-state structures with desirable properties based on the understanding of intermolecular interactions to dictate the arrangement of molecules in the crystal structure [48]. The concept of crystal engineering was first implemented by *Schmidt* [49] in 1971 and has now become an archetype for the synthesis for new compounds. When a compound is formed from non-covalent interactions, the molecules in the structure are held together by synthons. Hydrogen bonds are often utilized in cocrystal design due to their directionality, strength and frequency of occurrence in organic molecules. In 1991, E*tter* [50] proposed 3 rules for preferred hydrogen bond patterns: all available acidic hydrogen molecules will be used in the bonds formation, all hydrogen bond accepters will be used when there are available hydrogen bond accepters, and the best hydrogen bond donners and hydrogen bond accepters will form bonds to one another. It is the strength of the hydrogen bonds between the cocrystal formers, which govern the formation of synthons, as opposed to the number of available groups (Scheme 1). It is possible to predict and rank the possibility of synthon formation occurring between different functional groups, through utilizing these rules.

Essentially, synthons are the basic structural units within supermolecules, which form through non-covalent bonding and consist of molecular fragments and the supramolecular associations between them [51]. There are two types of supramolecular synthon: supramolecular homosynthons, composed of self-complementary functional groups and supramolecular heterosynthons composed of different but complementary functional groups [52]. Supramolecular heterosynthons are formed due to the non-covalent bonding between different, but complementary functional groups. It is the formation of the supramolecular heterosynthon between the API facilitates cocrystal formation [53]. Because of these rules, it is possible to theoretically predict and rank the possibility of synthon




**Scheme 1** Hydrogen bonding: a The indomethacin a-form. Two of the three symmetrically independent molecules form a carboxylic acid dimer synthon and the carboxylic acid group of the third molecule forms an O–H>O hydrogen bond with the amide carbonyl group of one of these two molecules. b The indomethacin g-form. The two molecules form a robust acid dimer synthon. c The carbamazepine–saccharin (CBZ–SAC) cocrystal contains an imide dimer synthon and forms N–H>O hydrogen bonds with the saccharin molecule. Reprinted with permission from 116.

formation between different functional groups. For example, a commonly occurring homosynthon is an amide homodimer forming a cocrystal through C=O··H–N hydrogen bond. Carboxylic acid-pyridine and carboxylic–amide. Are commonly occurring heterosynthons. This concept is employed in what is known as the supramolecular approach to cocrystal screening, where the Cambridge structural database (CSD) is also used to identify appropriate coformers for an API [54].

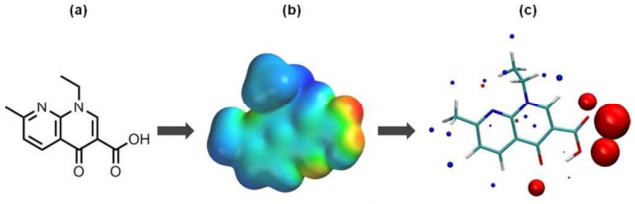
The CSD is a repository used to store data on molecular crystal structures. This is a validated tool to use in cocrystal screening as it prioritizes coformers, which can be used with a selective API based on whether or not a suitable supramolecular heterosynthon can be identified [55]. The CSD is well curated and updated with approximately 50,000 new structures added each year [56].

Because the physiochemical nature of the coformer effects that of the cocrystal, the coformer selection is a vital part of the pharmaceutical cocrystal design process. Traditionally, a trial and error approach was employed where the selected API would be synthesised with an array of pharmaceutically acceptable ingredients, however such an approach is expensive and inefficient [57]. Statistical analysis of cocrystal data on the CSD allows for research groups to apply virtual screening techniques to find appropriate cocrystal forming pairs, so cocrystals can be designed through molecular modelling, cutting both research time and experiment cost [58]. If molecules are able to interact through different, competing synthons, then a hierarchy must be established based on what the cocrystal is being designed to do. It must be known which synthons are formed at the expense of others. Numerous weaker interactions limit cocrystal design and using the CSD to identify and overcome any factors, beyond synthon forming which influence the failure or success of the cocrystal [52]. Through analysing the simple atom, bond and group counts, hydrogen bond donor and acceptor counts, size and shape descriptors, surface area descriptors (with partitioned and charge weighted variants), and molecular electrostatic descriptors and polarity descriptors of cocrystals found in the CSD, one can far more accurately predict the complementary of their cocrystal components [59-62]. It is possible to filter out any suspicious crystal structures, such as duplicates and incomplete structures from the CSD by using the *Van der streek* [63] list for best representatives of each unique polymorph, which further simplifying the process. In one specific example of this *Lemmerer et al.* [64] used the CSD to analyse the regularly occurring synthons for functional groups present in 2-chloro-4-nitrobenzoic acid and found that nicotinamide would form – forms hydrogen bonded C(4) chains from the H atom in the anti-position to the carbonyl O and from the he syn-H to the pyridine N to form C(6) chains. Through using molecular modelling calculations to examine the in the torsions angles in the crystal structures they were able to formulate a new cocrystal between 2-chloro-4-nitrobenzoic acid and nicotinamide.

Other methods of virtual screening have been demonstrated in literature. *Issa et al* [65] first attempted to predict the likelihood of cocrystal formation by comparing lattice energies of documented cocrystals with the sum of the lattice energies of their components. This idea was expanded upon by *Grecu et al* [66], where they developed a computational method for identifying API coformer pairs with a high chance of successfully forming cocrystals by calculating their functional group interactional energies. Using Nalidixic Acid as model API 44 of the most promising cocrystals were established from a library of 310, only 6 of which were known compounds. The other 38 where then ranked in order of probability. This was done by utilizing surface site interaction points (SSIP) which are calculated from the molecular electrostatic potential surface of the isolated molecule in the gas phase. The molecules interaction with its environment is then expressed via sets of SSIPs, each of which is represented by an interaction parameter. This is either positive for a hydrogen bond donor site or negative for a hydrogen bond accepter site. From this, the energy of interaction of the two SSIPs is presented, without the need of prior knowledge of the crystal structure. A Hierarchy between interactions can then be established by paring the most positive SSIP with the most negative, the second most positive with the second most negative and so on. This result indicates the potential of visual screening as a major tool in cocrystal development [66]. To further validate this method *Grecu et al* [54] tested this lattice energy screening model against experimentally screened cocrystals, in which the virtual cocrystal screen reproduces experimental results well, giving further credibility to this approach (Scheme 2).

Synthon matching is the key theory relied upon during cocrystal screening, but there are other factors which can determine the success of the cocrystal. One of the drawbacks of the computerized supramolecular synthon approach is that one cannot accurately predict the *in vivo* properties of the cocrystals. This is since the primary focus of the supramolecular synthon approach is to evaluate whether or not a hydrogen bond could exist between API and coformer and calculate the bonds strength and not on the physiochemical properties exhibited by API and coformer. One example for this is that after the synthesis of lamotrigine-nicotinamide cocrystals it was found that although the nicotinamide enhanced the solubility of lamotrigine it also possessed the ability to decrease the oral bioavailability [14].

One such method of experimentally screening for the experimental screening of cocrystals is by using thermal analysis. One way to do this is by studying the two components phase behaviour using Differential scanning calorimetry (DSC). With this method, a physical mixture of two potential cocrystal forming components are placed inside the DSC and heated beyond their point of eutectics. If cocrystallization is possible then an endothermic peak associated with the eutectic melting will be observed, immediately followed by an exothermic peak which indicates the cocrystallization of the two components. Another endothermic point will then be observed at the cocrystals melting point. By contrast, if cocrystallization is not possible between the two components, then a single endothermic peak indicating the eutectic melting is observed [67, 68]. It is the presence of the




**Scheme 2** (a) The chemical structure of nalidixic acid. (b) The DFT MEPS (density functional theory - molecular electrostatic potential surface) (red is negative and blue is positive). (c) The SSIP (surface site interaction points) representation (red is negative and blue is positive, and the size of the sphere is proportional to εi). Reprinted with permission from Ref. 124.

exothermic peak and second endothermic peak which indicates cocrystallization is possible. This technique was first demonstrated by *Lu et al.,* where DSC was used to screen twenty possible cocrystal forming systems. Sixteen cocrystals were formed, including nine previously undiscovered, demonstrating the DSCs potential for cocrystal screening [69]. This method of experimental screening is popular as it does not require the time consuming work of solubility determination and is considered green technology due to the absent of organic solvents [70]. However, in a 2014 comparative study by *Manin et al.,* [71] DSC was found to be the least effected thermal screening method giving many ambiguous results. For this reason, DSC is usually combined with hot stage microscopy (HSM) in order to allow the observation of cocrystal formation directly. The utilization of HSM is desirable as it allows the interpretation of ambiguous results [72]. It is also possible to combine DSC with Fourier-transform infrared spectroscopy (FT-IR) to establish the correlation between the thermal response and the structural changes of the sample [73].

Another method of thermal screening for cocrystals is by measuring the components saturation temperatures. First demonstrated by Joop *ter Horst* [10], this is accomplished by measuring situation temperature at a composition which correlates with the saturation, with respect to both of the cocrystal constituents at a reference temperature. If the saturation temperature is more than 10 ˚C higher than the reference, it indicates that cocrystallization has occurred. *Manin et al* [71] found the situation temperature method to be the most effective in cocrystal screening, compared to both DSC and HSM. However, it is also the most time consuming and requires the use of a solvent.

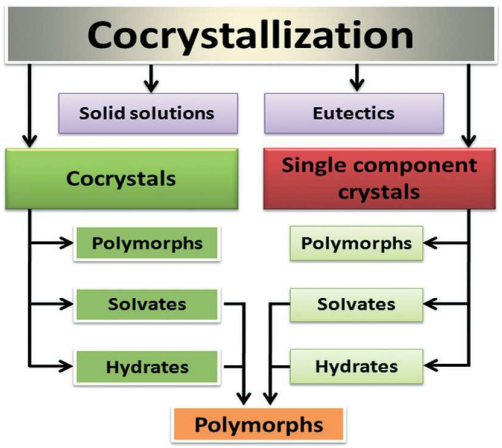
As previously mentioned HSM can be utilized in the screening of cocrystals by applying what is known as the kofler contact method. Using this method, the cocrystal constituent with the higher melting point, be it the API or coformer is melted and then allowed to solidify. The constituent with the lower melting point is also melted and placed in a contact zone with the other constituent. The solidified constituent is then dissolved in the liquid constituent, producing a mixing zone where the sample is quenched and then recrystallized. On either side of the mixing zone is the pure component of both of the cocrystal formers. The sample is heated once more until it reaches its melting point, under the HSM equipped with a polarizer. One can then view the newly formed cocrystal, beside the two pure components in the mixing zone. The cocrystal phase will retain birefringence and be distinguishable from the eutectic phase and the pure components, giving clear indication to whether or not cocrystallization was successful [64, 72, 73].

Another approach to experimental screening of cocrystals is by co-grinding. This approach involves mechanically grinding the cocrystal components together and observing whether cocrystals have formed through characterization techniques. Traditionally this can be achieved through either solid or liquid assisted screening methods. Liquid assisted screening have been proven to be most popular, with *Ainouz et al* [74] using this method along with computational prediction to assess the suitability of coformers with an API. Solid grinding can be viewed as preferable as there is no solubility limit influencing the system and there is no solvent present to disturb the interaction between the API and coformer. These methods however are incredibly time consuming. In an attempt to combat this, *Yamamoto et al* devised a "cocrystal cocktail method" where four coformers of identical moieties were ground simultaneously with the API in a ball mill, and characterisation carried out on the results in order to observe whether any of the coformers had reacted favourably with the API to produce cocrystals; this method was found to decrease the workload by 50 % [75].

Another theoretical technique, which has been utilized in coformer selection, is the Hanson solubility parameter (HSP). Predicting the miscibility of the cocrystal constituents by using the solubility parameters can indicate the likelihood of cocrystals forming. At a molecular level, cocrystals are miscible systems. Therefore, it is possible to predict the prospect of cocrystal formation based on the miscibility of the components in the solid state. If the difference between the solubility parameters of two entities is less than seven, then they are miscible and if the coformer is miscible with the API, cocrystallization should occur [76, 77]. This concept was investigated by *Mohammed et al* [78], where the miscibility for indomethacin and 33 coformers were calculated using HSP. From this, all except one of drug-coformers which were predicted to be miscible were experimentally confirmed as miscible. It was also found that all the indomethacin-coformer pairs that formed cocrystals were miscible. Although, one of the coformers that formed cocrystals demonstrated miscibility with the API, not all drug/coformer systems formed cocrystals. This can be due to lack of hydrogen bonding, preferred packing patterns and molecular shape and size, which this method does not allow for [78, 79].

## By-products in cocrystal screening

Cocrystallization has proven not to be a predictable process. For example, many API and coformer pairs, chosen based on potential synthon formation do not produce cocrystals. Often unwanted solid forms will be present after the cocrystallization experiment such as polymorphs, solvates, hydrates, eutectics, solid solutions or physical mixture (Scheme 3). The discovery of physical mixture in the batch is an indication that the cocrystallization has failed, as the bulk products have not reacted as desired. Crystalline solid solutions are single phase, multicomponent solids formed between isomorphous or isostructural materials, meaning that solid solutions form when both the API and coformer have the same type and positioning




**Scheme 3** Flow chart of potential outcomes of cocrystallization. Reproduced from Ref. 84 with permission from The Royal Society of

of functional groups and the same unit cell dimensions. Thus, solid solutions retain the lattice structure of the main component. The consequence of this is that the pharmaceutical properties of the API are not enhanced [80]. Eutectics are also multicomponent crystalline solids, except they are formed from non-isomorphous materials. This means there are size and shape differences between the two components and the hetromolecular interactions between the two components are weaker than that of a cocrystal, resulting in a lower melting point. In cocrystallization, the hetromolecular interactions will overcome the size and shape differences, resulting in a distinct crystal packing than that of the pure component's. In contrast, the packing arrangement of solid solutions and eutectics are similar to the original constituents [81].

One of the major downsides to liquid assisted grinding techniques for cocrystal production, which will be covered later in the review, is the potential for an unwanted solvate to form between the solvent and either the API or coformer. In one example, during a recent study by *Madusanka et al* [82] to Identify polymorphic forms of caffeine and anthranilic acid cocrystals via liquid assisted grinding, five different cocrystal solvates were formed with each of the solvents used.

Another potential unwanted outcome from cocrystal screening is hydrate formation. It is common for API to form a hydrate with water molecules due to their small size and multi-directional hydrogen bonding abilities [83]. In addition to altering the physiochemical properties of the desired product, the water molecules can escape the crystal lattice of the hydrate. This can occur at higher temperatures and at lower humidities, meaning hydrates are quite unstable. The physiochemical properties of the dehydrated form will differ from that of the hydrated form. Despite this cocrystal, hydrates are still an area of interest due to their resistance to high humidities, which can cause degradation in dehydrated forms. *Karki et al* demonstrated two techniques to screen for potential hydrates in cocrystallization; Liquid assisted grinding, using water as the solvent and solid state grinding with the hydrated form of the constituents. This study also demonstrated how different API are more susceptible to hydrate formation. The use of the hydrated form of theophylline, steered the reaction towards the formation of cocrystal hydrates, but this was not the case with hydrated caffeine, which formed cocrystals [121].

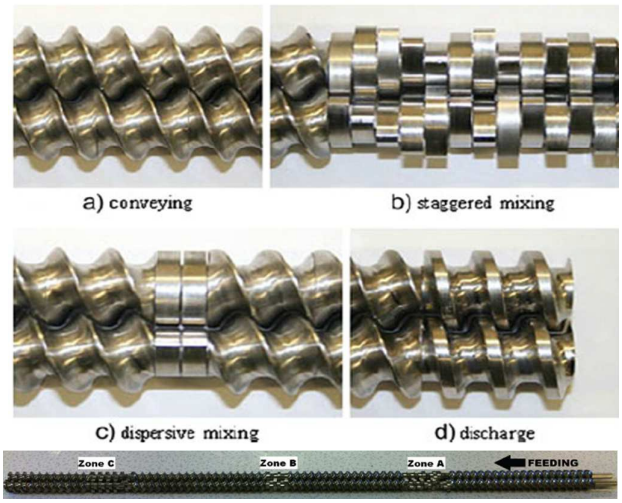
It is also possible for different polymorphs to form during the cocrystallization process. Polymorphism is the ability of a substance to exist in two or more crystalline forms, with different crystal lattice arrangements. Due to the differences in crystal lattice structure, different polymorphs present different physiochemical substances. Although they may still be a cocrystal, if one is screening for cocrystals, which display a certain beneficial property, obtaining a polymorph of the desired cocrystal, with different properties, can be seen as a setback. Therefore, screening for polymorphs of cocrystals is beneficial [84]. In one example *Eddleston et al* [85] obtained three anhydrous polymorphs, a monohydrate and a Dimethyl sulfoxide (DMSO) solvate from the screening of phenazine and mesaconic acid cocrystals. The study concluded that multi-technique approaches were necessary when screening for polymorphs in order to isolate the crystal forms.

## Hot melt extrusion

Hot melt extrusion (HME) is a novel technique that is gaining traction as a mechanism of producing pharmaceutical cocrystals. The technique was adapted from the rubber, plastics and food industries and is now seeing increasing use in the pharmaceutical industry [86]. The technique was first developed as a means of manufacturing lead pipes in the 18th century, though since then the process has been used in the production of plastic bags, pipes, pasta and palletised veterinary foods [87, 88]. So far, the primary applications of HME in the pharmaceutical industry include the production of solid dispersions using polymer or lip materials with the goal of modifying the properties of drug release [89]. Taste masking of bitter APIs [90] and increasing the solubility, dissolution and overall bioavailability of poorly water-soluble drugs [91]. HME has thus proved a versatile and adaptable process which is now accepted as a means of pharmaceutical synthesis due to the number of applications having been developed through HME processing, which includes pellets, tablets, granules, topical or buccal films, implants and recently the feasibility of combining HME with 3D printing technology to produce tablets has also been explored [92, 93]. Another key benefit in HMEs favour is that it meets the criteria of the US FDA's process analytical technology (PAT) scheme for designing, analysing and controlling the pharmaceutical manufacturing process via quality control measurements during active extrusion processing [94]. An example of drug formulations, developed by HME which have been awarded FDA approval include Rezulin, Kaletra and Norvir [95].

The HME process involves feeding raw materials through a barrel containing one or more rotary screws towards a die under controlled conditions. Immense friction takes place between the screw and barrel at high temperatures which provides good mixing of the raw materials, reducing particle size, thus creating cocrystals [96]. The instrument is principally divided into extruder, auxiliary equipment for extruder, downstream processing equipment and monitoring tools [97]. The temperature of each zone in the barrel is accurately controlled by a fixed thermostat and the screw is rotated using energy supplied by a motor unit. A die is attached to one end of the extruder to mould the processed material(s) into the desired shape.

One of the other key advantages of HME is that it is relatively simple to scale-up production to an industrial scale. The geometric similarities between mid-size and large scale HMEs enable rapid process scale-up without compromising product quality. Another advantage is that HME is a continuous process, which means it is more economical and reduces the number of processing steps when compared to other techniques, such as ball milling, making it more efficient as well [98, 99]. Because it is a continuous mechanism, the user is easily able to redesign the process to increase throughput and maintain acceptable quality at the same scale. The two most common variables during scale-up are barrel temperature and screw speed. Typically, as the batch size is increased the temperature must also increase. This is done to allow the increased product between the screws and the barrel wall to absorb the heat (Scheme 4). If temperature is not increased a percentage of the




**Scheme 4** Photographs of screw elements (a-c) used in various configurations (reprinted with permission from Ref. 98) and a typical twin – screw configuration (Reproduced from Ref. 103 with permission from The Royal Society of Chemistry).

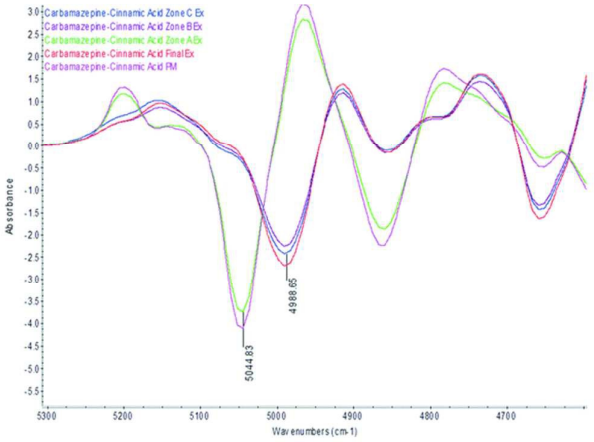
product may not be sufficiently heated and cocrystals will not form, resulting in a batch of poor purity. Screw speed must also be increased with the feed rate, otherwise the extruder will clog [99, 100].

Another key advantage is that real-time control, analysis and design optimization can be achieved using Process analytical tools (PAT) during the extrusion process. The purpose of this is to be able to assess the quality of the products by measuring their properties during the process. By using PAT during extrusion, it is possible to adjust the experiment parameters to improve the products quality hid-extrusion. In-line reflectance near infrared spectroscopy (NIR) is one analytical techniques commonly employed as PAT tools, with the purpose of understanding drug interactions and optimizing the process mid extrusion [101, 102]. Mordiya et al [91] demonstrated the first instance of PAT monitoring in HME where real time NIR monitoring was implemented during the extrusion of carbamazepine-saccharin cocrystals via extrusion. A fiber-optic NIR probe was fitted at three different zones along the extruder barrel (one at each mixing zone) in order to study the cocrystals formation in the extruder. It was found that cocrystallization of the two components starts in the first mixing zone due to the appearance of a cocrystal peak, which increases in size as the extrudate moves through the extruder barrel. This shows that cocrystals are formed gradually due to increased mixing capacity across the mixing zones. Mordiya et al [103] in the production of carbamazepine-trans-cinnamic acid cocrystals also utilized NIR as a PAT tools for cocrystallization via HME. Once again, the NIR probe was fitted at the 3 different mixing zones to monitor the cocrystallization process across the barrel. On this occasion, cocrystals did not first form until the second mixing zone and then continues to form gradually, indicating trans-cinnamic acid does not form hydrogen bonds with carbamazepine as readily as Nicotinamide (Scheme 5). This indicates that high intensity mixing has a significant effect on the quality of cocrystals, likely due to the breakage of solid domains, resulting in increased hydrogen bonding. This also proves NIRs capacity as an in-line, non-invasive PAT tool for cocrystallization via HME. As of yet no studies detailing the user of Raman spectroscopy or other PAT techniques for cocrystallization via HME have been reported.

There are two main types of extruder commonly available on the market: single screw (SSE) and twin-screw (TSE). SSE consists of a single screw contained within a spiral shaped barrel. The screws diameter increases along the length of the extruder shaft. The SSE is considered the simpler more cost effective potion and there are less processing parameters available to this option, such as less possible screw configurations and thus reduced mixing capabilities. TSE is built much the same as SSE with the primary difference being that of an extra screw. The two screws are placed parallel to one another in separate chambers within the same barrel. There is greater industrial interest in TSE due to the fact it provides greater mixing capabilities, high throughput and reduced residence time compared to the SSE. The screws can be set to either co-rotate (both screws rotate identically) or to counter rotate (screws rotate in opposite directions) [104, 105].

## Hot melt extrusion in pharmaceutical cocrystal production

The first instance of cocrystallization via HME was reported by *Medina, et al* [106]. Using a model drug AMG 517 and caffeine, they demonstrated that the TSE can provide suitable surface contact between the cocrystal components, due to the highly efficient mixing and close material packing, to produce cocrystals without using solvents. This research was expanded upon by *Dhumal et al* [107], who explored the effects of different processing parameters of HME in the manufacture of agglomerated cocrystals of ibuprofen and nicotinamide. They achieved this by employing a quality based design approach, by extruding a 1:1 molar ratio of ibuprofen and nicotinamide at variable screw speeds, temperature profiles and with different screw configurations. It was found that the barrel temperature must be above the eutectic point of the physical mixture for cocrystallization to occur and demonstrated the extent of how the processing parameters affected the purity of the cocrystals. Screw configuration was found to have the most significant effect on the cocrystallization, with the highest sheer configuration producing the purer cocrystals.

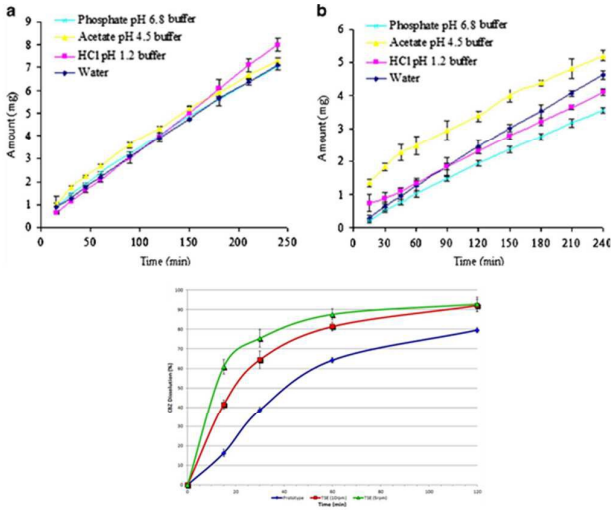



**Scheme 5** Second derivative of in-line NIR spectra in the mixing zones (A, B, and C) of extruded cocrystals in a twin – screw extruder and the physical mixture. Reproduced from Ref. 103 with permission from The Royal Society of Chemistry.

In 2011, *Daurio et al* [108], attempted to further demonstrate the potential of HME suitable mechanism for manufacturing cocrystals on an industrial scale. Arguing that TSE is easily scalable and highly efficient way to produce cocrystals, due to the fact the process is continuous, they set out to demonstrate this using four model cocrystals: caffeine-oxalic acid, nicotinamide-trans cinnamic acid, carbamazepine-saccharin and theophylline-citric acid. These cocrystals were selected since they had been extensively studied in literature and could be easily compared with other cocrystallization methods. These results indicated that HME was successful in producing high purity batches for all four cocrystals tested.

*Daurio et al* [108], was also able to observe the effects of HMEs extrusion parameters on the overall conversion of the cocrystal batch. When extruding the Caffeine-Oxalic acid cocrystals at the same temperature with different screw designs, it was found that the design, which allowed for greater mixing provided a higher conversion from the bulk products to the cocrystal. Similarly, the effect of residence time was demonstrated where X-Ray Powder Diffraction (XRPD) data indicated incomplete conversion to cocrystals that were extruded at higher screw speeds. When the Caffeine-Oxalic acid cocrystals analysed, temperature was the only variable parameter with little mixing taking place showed poor conversion rates, thus indicating this particular cocrystal to be more dependent on residence time and screw configuration. This is in stark contrast to the nicotinamide-trans cinnamic acid cocrystal, where the extent of cocrystallization, seemed to be primarily dependent on temperature. The results for the carbamazepine-saccharin and theophylline-citric acid were also shown to increase in purity as the processing parameters were optimized. Using the carbamazepine-saccharin cocrystals as an example, the total processing time to produce cocrystals through HME was recorded between 2-5 min. In contrast, the ball milling mechanism to produce cocrystals has a reported residence time of over 30 min [108, 109].

To demonstrate the effectiveness in improving the solubility of poorly water soluble drugs using HME, *Moradiya et al* [91], synthesised carbamazepine-saccharin cocrystals using both a SSE and TSE. Theoretically the TSE would provide better mixing over the SSE. DSC results showed far broader peaks for the cocrystals created using the SSE in comparison to the cocrystals produced via TSE, indicating a reduced purity/less conversion. The dissolution profile showed that the carbamazepine-saccharin cocrystals produced via TSE dissolved in water faster than those produced via SSE. This suggests that improved mixing is essential to the conversion rate of cocrystals and is a key parameter in enhancing the solubility of the cocrystal. It is also worth noting that the batches produced at a higher temperature presented a quicker dissolution time, demonstrating the extrusion temperatures effect on cocrystal solubility. In another example, carbamazepine-*trans*-cinnamic acid cocrystals were extruded by both SSE and TSE. DSC and XRPD results showed less crystallinity for the cocrystals produced via SSE when compared to those produced by TSE. Again, dissolution studies showed that TSE processing produced cocrystals with a faster dissolution rate when compared to those produced by SSE, demonstrating the effect of increased mixing on cocrystal solubility [95, 110] (Scheme 6).




**Scheme 6** Intrinsic dissolution profile of Carbamazepine (a) and Carbamazepine - Nicotinamide cocrystals (b) in different media (Reprinted with permission from Ref. 24) and dissolution profiles (0.1 N HCl, pH 1.2) of Carbamazepine – Saccharin prototype (MeOH, EtOH solvents), CBZ-SCH cocrystals processed with twin – screw extrusion at 5rpm and 10rpm respectively (reprinted with permission from Ref. 91).

Hot-melt extrusion techniques have been demonstrated to be advantageous when working with heat labile drugs. When exposed to high temperature, a number of drugs begin to thermally degrade. *Liu et al* [111], combined carbamazepine, a heat sensitive API, with nicotinamide to form cocrystals to act as a model drug to process using HME technology, with the aim of demonstrating cocrystallization as a useful strategy to avoid thermal degradation during HME. This cocrystal was co-extruded alongside polymers; PVP/VA, Soluplus and hydroxypropyl methylcellulose (HSPM). The aim of this was to assess the feasibility of cocrystalizing carbamazepine to make it more thermodynamically stable during the HME process, while being co-extruded with a polymer. The melting point of carbamazepine-nicotinamide cocrystals is 160° which is significantly lower than melting point of bulk carbamazepine. The results showed that it is possible to successfully prepare amorphous carbamazepine-nicotinamide-polymer solid dispositions while extruding at a temperature far below that of the bulk substances, thus preventing heat damage. Nicotinamides great solubility also leads to a more soluble cocrystal, thus indicating greater bioavailability [112].

Another study by *Boksa et al.* [113], attempted to further improve the solubility of carbamazepine-nicotinamide cocrystals through adding the polymer Soluplus. This was done through a technique dubbed; matrix assisted cocrystallization, where co-processing the API and coformer in the presence of a matrix. In this case the cocrystal products and Soluplus matrix was co-extruded at an 80:20 (w/w) ratio. The matrix assisted cocrystal was found to dissolve faster than the reference cocrystal, indicating that coextruding offers significant solubility benefits.

In a 2014 study, *Daurio et al* [114] demonstrated HMEs potential as a viable production process for the scale-up of production of cocrystals. By employing AMG 517–sorbic acid cocrystals as a model drug, the extrusion parameters which effect the purity of cocrystals

were investigated (e.g. temperature, feed rate, residence time, screw configuration). The extruded cocrystals were then compared with solution grown cocrystals. The results suggested that, contrary to previous literature, the eutectic formation did not mediate cocrystal formation in the extruder. However, temperature was still found to be a main parameter in dictating cocrystal conversion, along with screw configuration. Feed rate and residence time was discovered to exert a moderate influence on cocrystallization. The TSE approach was found to exert improved surface area, bulk density, and flow properties when compared to the solvent cocrystallization methods. This further indicates that HSE is an efficient, continuous and easily scalable cocrystal production method. Below, alternative solid state mechanisms to synthesise cocrystals are described.

One of the persistent issues presenting a challenge to industrial uptake of pharmaceutical cocrystals is that of reproducible stoichiometry control. It is possible to produce increase the number of cocrystal solid forms by using different stoichiometric ratios. However, synthesizing different stoichiometries greatly complicates the cocrystallization process in most cases. For example, using grinding techniques Trask et al [27] found that it was not possible consistently reproduce caffeine-malic acid cocrystals of different stoichiometries, without the use of a solvent. In another instance Karki et al [119] attempted to produce cocrystals of different stoichiometries using Nicotinamide API and 10 different dicarboxylic acid coformers. This was attempted using solution techniques as well as solid state, liquid assisted and melt assisted grinding. Results indicated that approximately 50 % of cocrystals produced by solution techniques, 40 % of cocrystals produced via melt assisted grinding and only 25 % of cocrystals produced via solid state and liquid assisted grinding corresponded to the stoichiometry of the starting materials. However, recent research by Kulkarni et al [122] has indicated that stoichiometric control over cocrystals is achievable through HME. Caffeine/Maleic acid cocrystals as a model drug it was demonstrated that by extruding a 2:1 mixture of Caffeine-malic acid, it is possible to control the stoichiometry of the final product by simply editing the temperature settings. If the 2:1 mixture was processed below 104 °C then the formation of a 1:1 cocrystal is favoured. If the extrusion temperature exceeds 104 °C then the 1:1 cocrystal will melt and the components will form a 2:1 stoichiometric cocrystal. This indicates that stoichiometric control over cocrystals is possible through editing the extrusion parameters of HME, without having to edit the initial batch or switch cocrystallization technique. This is a major advantage for HME processing as limiting the production steps equates to greater efficiency and reduced cost.

## Grinding methods for cocrystallization

There are two commonly utilized mechanisms to synthesize cocrystals via grinding. The first is solid state grinding, also known as dry grinding, where the cocrystal components are simply ground together through manual or mechanical processes. The second is liquid assisted grinding, also called solvent drop, where a small amount of liquid is added to the mixture to act as a catalyst [115]. The advantages of solid state grinding to form cocrystals, when compared to solution based methods, was presented by *Patil et al* [116], who demonstrated that the grinding of mixtures was superior to solution growth. This was expanded on by *Etter et al* [50] who demonstrated how the grinding of solids, would cause hydrogen bonding of adenine and thymine. These methods were simply carried out through manual grinding, which presents the problem to the scale up of production, so different mechanical methods must be used for efficient cocrystal production. One solid state grinding method to form cocrystals is by employing the use of ball milling, where particle size reduction is carried out by impact as the cocrystal components are loaded into a rotating chamber partially filled with steel balls. In one example, *Trask et al* [117] utilized grinding via ball milling to synthesize caffeine cocrystals with several different dicarboxylic acids, were 5 different caffeine based cocrystals were synthesised.

Solid state grinding has been used to produce metastable polymorphs of cocrystals. *Aitipamula et al* [118] Used solid state grinding techniques to investigate the synthesis of cocrystal polymorphs. Through ball milling a 1:1 stoichiometric ratio of ethenzamide-Saccharin cocrystal, it was possible to produce two polymorphs of the cocrystal. Analysis of the crystal structure revealed that both polymorphs were comprised of amide-imide supramolecular heterosynthons. These two polymorphs were previously unattainable using solvent based cocrystallization methods. The study concludes that to capture all possible cocrystal polymorphs a diverse range of synthesis techniques including solid state grinding.

Solid state grinding techniques have also been shown to be effective in the formulation of cocrystals of stoichiometric variation. Stoichiometric variation describes cocrystals composed of the identical constituents, which are present in differing ratios. This was demonstrated by *Karki et al* [119], who argued that solid state grinding methods are more efficient than solvent based methods, such as solvent evaporation, as the formation of stoichiometric variations are easily controllable by modifying the composition of the reaction mixture. This was demonstrated by ball milling Nicotinamide as a model API with suberic acid, in either 1:1 or 2:1 ratio to form nicotinamide-suberic acid cocrystals. The results showed grinding techniques allow for greater control of cocrystal composition when compared to synthesis techniques requiring liquids. Solid state grinding techniques for the synthesis of cocrystals of variable stoichiometric ratios had previously been reported by *Vishweshwar et al* [120].

Liquid assisted grinding can be carried out when there is no sign of the formation of a new phase. Liquid assisted grinding will often incorporate the use of a small amount of solvent to act as a catalyst for the cocrystallization process. To demonstrate the solvents effect, *Trask el al* [117] applied liquid assisted grinding to the synthesis of caffeine based cocrystals which were unable to fully crystalize through solid state grinding methods. Through the addition of solvent of cocrystallization of the caffeine, based drugs took place. This form of grinding carries the same inherent issues as solid state grinding; however, there is the added issue of solvent disposal with liquid assisted grinding along with the potential risks to the environment.

In 2007, *Karki et al* [121] attempted to compare the solid state and liquid assisted grinding techniques for the screening and preparation of hydrated cocrystals, using theophylline and Caffeine as a model API. In this study, it was found that liquid assisted

grinding is less sensitive to the form of reactants (hydrate or anhydrite) than the neat grinding mechanism, so it was concluded that liquid assisted grinding is better suited for cocrystal screening. In another comparison between the two methods, *Rehder et al* [122] used a solid state grinding to process piracetam-citric acid and piracetam-tartaric acid using an oscillatory ball mill. In comparison with the solvent drop technique, solid-state formulation of the cocrystals was found to be slower and displayed reduced crystallinity. This was explained to be because of the higher molecular mobility of the API and coformer as a result of their partial solubility in the solvent. This contrasts with the findings of *Viertelhaus et al* [123], observed a loss in crystallinity in Piracetam-citric acid cocrystals prepared using the same liquid assisted grinding method. However, solid state grinding was still found to be the slower than liquid assisted, taking up to 10 min to complete the process.

With the objective of investigating the feasibility of forming cocrystals through green chemistry methods *Basavoju et al* [124] utilized solid state grinding to form indomethacin and saccharin cocrystals. Cocrystallization was successfully carried out for both solid state and liquid assisted grinding, though with liquid assisted grinding the added issue pertaining to the disposal of the solvent was encounter. As previously stated can cause potential environmental harm, which arguably disqualifies this technique as green chemistry.

One of the main drawbacks with solid state grinding is that there is no heating stage involved in the process. Numerus studies have reported the importance of temperature in the cocrystallization process, and lacking that component, far more energy is required to induce cocrystallization by grinding alone [78, 108, 109-112]. One method to overcome this is the induction of a solvent as a catalyst to assist the extrusion process. There has been a decrease in research into solid-state grinding methods, to induce cocrystallization due to numerus papers demonstrating liquid assisted grindings superiority [121-123, 130]. In a comparative study, Friščić et al [115], attempted to form cocrystals of theophylline and caffeine trough solid state grinding, liquid assisted grinding and sonic slurry methods. Theophylline-L-malic cocrystals were the only success using solid state grinding methods out of the four possibilities tested. The study also found that the Theophylline-L-malic cocrystals produced through solid state grinding had an inferior degree of crystallinity than those prepared by liquid assisted grinding.

However, this disqualifies it as green chemistry and adds the extra cost of using and disposing of the solvent, especially during large scale production. Another drawback for liquid assisted grinding that there could potentially be large differences in the solubility of the API and coformer rendering this method difficult to perform and in some cases impossible [125]. There is also the added problem that the interactions between the solvent and the API or coformer could disturb the interactions between the cocrystal constituents. The addition of solvent can lead to the formation of unwanted cocrystal solvates [82]. For this reason, it can be argued that the addition of solvents in cocrystal synthesis are an unnecessary complication as well as being a costlier and environmentally unfriendly. Therefore, HME is a preferable choice of method, as it combines the heating and grinding steps, while not requiring the use of a solvent to induce cocrystallization, therefore qualifying as a green method of preparing cocrystals. Another limitation of grinding approaches to cocrystallization is that they are far less efficient and costlier compared to HME. As there are more processing steps involved and the process is not continuous, it will take longer to synthesize cocrystals, especially if manual grinding techniques are used. With HME the cocrystal components are continuously fed into the extruder, meaning the process is automatic and can be adjusted at short notice, something which cannot be done through grinding. This leads into another big drawback that it is difficult to scale up production using grinding methods. Due to the uniformity and continuous nature HME, it is relatively simple to scale up production, without editing too many processing parameters. With the addition of PAT technology, it is also possible to evaluate cocrystal quality in line and edit the temperature, screw speed and feed rate accordingly to accommodate scale up and address any issues immediately. Grinding techniques do not have this luxury. Cocrystals can only be characterised post production and if there are any issues present, then the process must be repeated from the start. All these issues equate to extra labour and processing time, with equal extra costs [75-77, 108-113].

## Melt assisted grinding

One technique which has been attempted in order to overcome solid state grindings pitfall of not involving a heating stage, while also not requiring the use of a solvent, is melt assisted grinding. In this technique, a physical mixture of the API and coformer will be heated until the melting point, then slowly cooled for cocrystallization to take place. This method is similar to HME, in regards to the fact the constituents are heated together to achieve cocrystallization, but advantage HME holds over melting method is additional shear force and increased mixing. To demonstrate this method, as a means of cocrystallization with reduced melting temperatures *Liu et al* [111] synthesized Carbamazepine-Nicotinamide cocrystals and compared the results to the same cocrystals produced via HME. To achieve the melting, the two base components were placed on a hot plate and heated at 160˚C and then cooled slowly at ambient conditions. The cocrystals were then crushed via mortar and pestle and passed through an 80-mesh sieve. The aim of the study was to produce Carbamazepine-nicotinamide cocrystals at low temperatures to avoid thermal degradation and in this regards the melting assisted cocrystallization method was successful as pure and stable cocrystal were produced. The HME produced cocrystals showed better dissolution properties. In another example *Rahman et al* [24], utilized melting assisted grinding to produce Carbamazepine-nicotinamide cocrystals. This was achieved by melting the base products on a paraffin oil bath at 140°C for 10 min and then cooled at room temperature. The cocrystals then were powdered by a mortar and pestle and passed through 60 mesh sieve. Though cocrystals were produced, analysis by SEM showed the cocrystals to be irregularly shaped, likely due to the crushing process following cooling. DSC analysis also showed that the cocrystals produced by this method contained some amorphous material in the batch. This method is a limited approach when compared to other techniques as it was shown to reduced quality cocrystals and there is also the inherent issue with the scale up using this method [24, 111]. HME is a continuous process, where the bulk products can be constantly fed

through, into the extruder with the products being heated through the barrel. This is not possible with melt, assisted grinding as all components must be loaded onto the hot plate/ heating bath prior to the processes commencement. There are also added production steps, in HME the heating and grinding steps both take place in the extruder barrel, whereas these are two separate steps using melt method. They must first be heated, cooled and then crushed, meaning HME is far more efficient.

## Regulatory perspectives of pharmaceutical cocrystals

This article has demonstrated cocrystals pharmaceutical potential in drug development, so the next logical step would be gaining regulatory approval, to standardize how the growing drug types can be brought to market. However, there have been a number of issues preventing this. Over the last decade, as interest in cocrystal development had been growing, there have been a number of compositions of matter patents acknowledged for cocrystals. This has been on the basis that the cocrystals in question display the primary criteria for issuing a patent. These are the cocrystal is of a new molecular composition (not similar to the molecular structure of other drugs), there is a degree of 'non- obviousness' that means the physiochemical properties of the cocrystals are not easily predicted, and the new cocrystal must offer an advantage over the single component drug. This means that the new cocrystal must have certain enhanced properties which give it an edge over the bulk substance. This is done so that one drug development company cannot release a structurally different, but essentially analogous in function. Allowing this would allow the new substance to directly compete with the single component drug [126].

The FDA released guidelines for the pharmaceutical industry in 2011 pertaining to the patenting of cocrystals. Within these guidelines cocrystals were classed as an 'API excipient' molecular complex, a drug product intermediate and not a new API. This presented a problem for cocrystal development as an intermediate in drug development is not afforded the same benefits as a new API. In the document the FDA does not rank cocrystals in the same league as salts and polymorphs. The FDA required that a further two criteria be met before product approval would be granted, which were that API and excipient must completely dissociate prior to reaching the pharmacologically active site and also that he API and excipient are in neutral states and do not interact by ionic bonds.

A perspective article was published as a response to this FDA ruling [127]. This article argued that the only difference between a crystalline salt and a cocrystal lies merely in the transfer of a proton from one component to the other, which is dependent on temperature [12, 127]. Due to the fact that many drugs on the market are considered by many to be cocrystals, pharmaceutical companies lobbied the FDA with the opinion that cocrystals should be treated as salts, if not awarded their own subclass. Two examples of these are Depakote®, which contains sodium valproate–valproic acid and Caffeine citrate [128, 129].

In contrast to the FDAs position on the regulatory status of cocrystals; in 2015, the European Medicines Agency (EMA) released a reflection paper on summarising their position on the use of cocrystals of API in medicine [130]. The paper states that the FDA believes cocrystals to be *"homogenous (single phase) crystalline structures made up of two or more components in a definite stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds (as with salts)".* The paper concludes that cocrystallization is a viable alternative to salt formation and a method of achieving more solid state matter with unique properties [130]. The EMA state that as cocrystals and salts share a number of conceptual similarities, they should undergo similar principals of documentation as salts [81]. Although the FDA and EMA currently occupy very different viewpoints on the subject of the regulation of pharmaceutical cocrystals, the fact that both agencies have released guidelines for the industry to follow demonstrates the growing interest in the use of pharmaceutical cocrystals as potential marketable drugs.

## Future developments and remaining challenges

As previously stated, one of the biggest limitations to the growth of cocrystals in the pharmaceutical industry is their current classification under regulatory guidelines. This is most prevalent in the United States, as while cocrystals are classified as an API excipient, there is little monetary gain cocrystal production. This is due to the fact that new cocrystal products are difficult to patent. Other challenges, which need to be addressed, include the stability of cocrystals in the presence of excipients, which is currently a relatively unexplored area. There are also the issues pertaining to the scale up, which currently make cocrystals an unattractive option to industry due to the fact mass production which is difficult.

Despite this, research into cocrystals continues to grow and as more drug products that are based on cocrystal research hit the market, it can only be expected for pharmaceutical cocrystals to gain a stronger grip in drug development. The recently published reflection paper by the EMA states that cocrystals will be granted the status of new active substance if their efficacy and safety is proved [130]. The recent phase II success of tramadol and celecoxib co-crystals, a drug-drug cocrystal is a further sign that cocrystal development is advancing. In a 2014 article *Blagden et al* [132] cited current physical screening techniques as one of the key barriers in preventing cocrystal utilization due to the fact it is difficult to automate a high throughput screening technique. *Blagden et al* postulated that advancements in computational screening approaches would see further utilization of cocrystals as pharmaceutical products [132]. Recently developed software by the Cambridge Crystallographic Data Centre (CCDC) such as Cambridge Structural Database (CSD)-materials and CSD discovery provides software tools to assist in the intra-molecular interactions within the crystal lattice and in the discovery of new crystal forms respectively [133]. These advancements' along with improvements in scoring systems for cocrystal prediction [134] and advancement's in hydrogen bonding research should help facilitate advancement's in computational modelling [135].

As has been previously explained in this article, HME demonstrates great potential to combat the issue related to the scale-up of cocrystallization and has already been demonstrated too do so [102, 114]. In a recent paper, *Boksa et al* [113] successfully developed a method of polymer-assisted cocrystallization using HME to produce high quality cocrystals. This was achieved by embedding the cocrystals in 20 % soluplus. This method is solvent free, scalable and was shown to be amenable to continuous

manufacturing, making it an area of great interest for future research. A similar method was employed by *Basa et al* using a polymer assisted grinding technique to synthesise caffeine-citric acid cocrystals. Six different alongside poly(ethylene glycol) polymers were used in this study and the results were compared to liquid assisted grinding methods. The results showed that polymer-assisted grinding compared favourably to the liquid assisted methods, whilst also eradicating the risk of unwanted solvent formation [136].

Other potential areas for further research in cocrystallization via HME relate to the use of potential PAT monitoring systems which have been utilized in other elements of HME production and could be used for cocrystals. For example, *Saerens et al* has successfully utilized Raman spectroscopy as an in-line monitoring tool for in HME for the extrusion of drug-polymer mixtures. In this case in-line Raman monitoring allowed for the influence of changes in the die pressure to be monitored. This can be translated to cocrystal research and can be used to assess the impact of temperature and screw configurations [137]. *Treffer et al* has implemented in-line image based particle size analyses tools in HME, in order to monitor the particle properties of extruded pellets. This could potentially be incorporated in cocrystal extrusion to examine the effect of process parameters on cocrystal particle size and surface properties [138].

## Conclusions

Research in pharmaceutical cocrystals will continue to grow as coformer-screening strategies become more simplified. Industrial interest in pharmaceutical cocrystals will continue to grow due to the enhanced pharmaceutical benefits they exhibit and because of the decreased drug development time it should take cocrystals to reach the market, due to aspects such as toxicology already being known. Recent advances in cocrystal engineering involve virtual computational screening while solid-state approaches for cocrystal synthesis appear to be attractive compared to solvent crystallization. HME is now widely recognized as a viable method to create pharmaceutical cocrystals due to the fact it is continuous, solvent-free, cost efficient offers reduced production times, has fewer processing steps and quality assurance can be easily monitored. Nevertheless, there are several hurdles to overcome before pharmaceutical cocrystals are commercially fully exploited.

## References

1. F. Wohler, *Annalen der Chemie und Pharmacie*, 1844, **51**, 145-163.
2. M. Goldman, Z. Kustanovich, S. Weinstein, A. Tishbee and E. Gil-Av, *J. Am. Chem. Soc.*, 1982, **104**, 1093-1095.
3. G. Stahly, *Cryst. Growth Des.*, 2009, **9**, 4212-4229.
4. A. Nangia and N. Rodríguez-Hornedo, *Cryst. Growth Des.*, 2009, **9**, 3339-3341.
5. S.L. Childs and M.J. Zaworotko, *Cryst. Growth Des.*, 2009, **9**, 4208-4211.
6. J. Dunitz, *CrystEngComm*, 2003, **5**, 506.
7. T. Friščić, T, Jones W, *Cryst. Growth Des.*, 2009, **9**, 1621-1637.
8. A. Bond, *CrystEngComm*, 2007, **9**, 833.
9. FDA. Guidance for Industry: Regulatory Classification of Pharmaceutical Cocrystals [Internet]. 2013[cited 17 January 2016]. Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm281764.pdf.
10. J. ter Horst, M. Deij and P. Cains, *Cryst. Growth Des*, 2009, **9**, 1531-1537.
11. N. Duggirala N, Perry M, Almarsson Ö, Zaworotko, *Chem. Commun.*, 2016, **52**, 640-655.
12. S. Aitipamula, R. Banerjee, A. K. Bansal, K. Biradha, M. L. Cheney, A. R. Choudhury et al*, Cryst. Growth Des.*, 2012, **12**, 2147.
13. N. Qiao, M. Li, W. Schlindwein, N. Malek, A. Davies and G. Trappitt, *Int. J. Pharm.*, 2011, **419**, 1-11.
14. P. Vishweshwar, J. McMahon, J. Bis and M. Zaworotko, *J. Pharm. Sci.*, 2006, **95**, 499-516.
15. B. Sekhon, *ChemInform*, 2013, **44**.
16. I. Tomaszewska, S. Karki, J. Shur, R. Price and N. Fotaki, *Int. J. Pharm.*, 2013, **453**, 380-388.
17. I. Miroshnyk, S. Mirza and N. Sandler, *Expert Opin. Drug Deliv.*, 2009, **6**, 333-341.
18. M. Stanton and A. Bak, *Cryst. Growth Des.*, 2008, **8,** 3856-3862.
19. S. Childs, L. Chyall, J. Dunlap, V. Smolenskaya, B. Stahly and G. Stahly, *J. Am. Chem. Soc.*, 2004, **126**, 13335-13342.
20. Fda.gov, 2016.
21. N. Schultheiss and A. Newman, *Cryst. Growth Des.*, 2009, **9,** 2950-2967.
22. X. Wang, Q. Zhang, L. Jiang, Y. Xu and X. Mei, *CrystEngComm*, 2014, 16, 10959-10968.
23. S. Alshahrani, W. Lu, J. Park, J. Morott, B. Alsulays, S. Majumdar, N. Langley, K. Kolter, A. Gryczke and M. Repka, *AAPS PharmSciTech*, 2015, **16**, 824-834.
24. Z. Rahman, C. Agarabi, A. Zidan, S. Khan and M. Khan, *AAPS PharmSciTech*, 2011, **12**, 693-704.
25. P. Hsu, H. Lin, S. Wang and S. Lin, *J. Solid State Chem.*, 2012, **192**, 238-245.
26. M. Hickey, M. Peterson, L. Scoppettuolo, S. Morrisette, A. Vetter, H. GuzmÃ¡n, J. Remenar, Z. Zhang, M. Tawa and S. Haley, *Eur. J. Pharm. Biopharm.*, 2007, **67**, 112-119.
27. A. Trask, W. Motherwell and W. Jones, *Cryst. Growth Des.*, 2005, **5**, 1013-1021.
28. A. TRASK, W. MOTHERWELL and W. JONES, *Int. J. Pharm.*, 2006, **320**, 114-123.
29. C. Sun and H. Hou, *Cryst. Growth Des.*, 2008, **8**, 1575-1579.
30. S. Chow, M. Chen, L. Shi, A. Chow and C. Sun, *Pharm Res*, 2012, 29, 1854-1865.
31. M. Lindenberg, S. Kopp and J. Dressman, *Eur. J. Pharm. Biopharm.*, 2004, **58**, 265-278.
32. R. Thakuria, A. Delori, W. Jones, M. Lipert, L. Roy and N. Rodriguez-Hornedo, *Int. J. Pharm.*, 2013, **453**, 101-125.
33. D. Good and N. Rodriguez-Hornedo, *Cryst. Growth Des.*, 2009, **9**, 2252-2264.
34. S. Qiu and M. Li, *Int. J. Pharm.*, 2015, **479**, 118-128.
35. S. Childs, N. Rodríguez-Hornedo, L. Reddy, A. Jayasankar, C. Maheshwari, L. McCausland, R. Shipplett and B. Stahly, *CrystEngComm*, 2008, **10**, 856.
36. C. Maheshwari, V. André, S. Reddy, L. Roy, T. Duarte and N. Rodríguez-Hornedo, CrystEngComm, 2012, **14**, 4801.
37. A. Alhalaweh, L. Roy, N. Rodríguez-Hornedo and S. Velaga,

Mol. Pharmaceutics, 2012, **9**, 2605-2612.
38. D. Serrano, P. O'Connell, K. Paluch, D. Walsh and A. Healy, *J. Pharm. Pharmacol.*, 2015, doi: 10.1111/jphp.12476.
39. A. Yadav, A. Shete, A. Dabke, P. Kulkarni and S. Sakhare, *Indian J. Pharm. Sci.*, 2009, **71**, 359.
40. Eli lilly patent: US5412094 (A1), JP7048383 (A), FI943081 (A), BR9402561 (A) and EP0637587 (B1), 1995
41. A. Trask, *Mol. Pharmaceutics*, 2007, **4**, 301-309.
42. J. Lindeman, *Pharm Pat Anal*, 2012, **71**, 513-515.
43. N. Shan and M. Zaworotko, *Drug Discov Today*, 2008, **13**, 440-446.
44. M. Cheney, M. Zaworotko, S. Beaton and R. Singer, *J. Chem. Educ.*, 2008, **85**, 1649.
45. G. Bruni, M. Maietta, V. Berbenni, P. Mustarelli, C. Ferrara, M. Freccero, V. Grande, L. Maggi, C. Milanese, A. Girella and A. Marini, *the J. Phys. Chem. A B*, 2014, **118**, 9180-9190.
46. H. Brittain, *Polymorphism in pharmaceutical solids*, Informa Healthcare, New York, 2009.
47. Viagra-Aspirin patent: Zegarac M, Mestrovic E, Dumbovic A, et al. Pharmaceutically acceptable cocrystalline forms of sildenafil. WO 2007/080362 A1, 200748.G. Desiraju, *Int Union Crystallogr J*, 2014, **1**, 380-381.
48. C. Aakeröy, N. Champness and C. Janiak, CrystEngComm, 2010, **12**, 22-43.
49. G. Schmidt, *Pure and Applied Chemistry*, 1971, 27.
50. M. Etter and S. Reutzel, *J. Am. Chem. Soc.*, 1991, **113**, 2586-2598.
51. G. Desiraju, *ChemInform*, 2008, 39.
52. M. Hemamalini, W. Loh, C. Quah and H. Fun, *Chem Cent J*, 2014, **8**, 31.
53. P. Wood, N. Feeder, M. Furlow, P. Galek, C. Groom and E. Pidcock, *CrystEngComm*, 2014, **16**, 5839.
54. T. Grecu, C. Hunter, E. Gardiner and J. McCabe, *Cryst. Growth Des.*, 2014, **14**, 165-171.
55. C. Groom and F. Allen, *Angewandte Chemie International Edition*, 2014, **53**, 662-671.
56. I. Bruno and C. Groom, *Journal of Computer-Aided Molecular Design*, 2014, **28**, 1015-1022.
57. S. Morissette, *Adv. Drug Deliv. Rev.*, 2004, **56**, 275-300.
58. V. Hathwar, T. Thakur, T. Row and G. Desiraju, *Cryst. Growth Des.*, 2011, **11**, 616-623.
59. F. Allen and W. Motherwell, *ChemInform*, 2010, 33, no-no.
60. A. Delori, P. Galek, E. Pidcock, M. Patni and W. Jones, *CrystEngComm*, 2013, **15**, 2916.
61. A. Moragues-Bartolome, W. Jones and A. Cruz-Cabeza, *CrystEngComm*, 2012, **14**, 2552.
62. T. Thakur and G. Desiraju, *Cryst. Growth Des.* , 2008, **8**, 4031-4044.
63. J. van de Streek, *Acta Crystallogr Sect B*, 2006, **62**, 567-579.
64. A. Lemmerer, C. Esterhuysen and J. Bernstein, *J. Pharm. Sci.*, 2010, **99**, 4054-4071.
65. N. Issa, P. Karamertzanis, G. Welch and S. Price, *Cryst. Growth Des.*, 2009, **9**, 442-453.
66. T. Grecu, H. Adams, C. Hunter, J. McCabe, A. Portell and R. Prohens, *Cryst. Growth Des.*, 2014, **14**, 1749-1755.
67. H. Yamashita, Y. Hirakura, M. Yuda, T. Teramura and K. Terada, *Pharm Res*, 2012, **30**, 70-80.
68. H. Yamashita, Y. Hirakura, M. Yuda and K. Terada, *Pharm Res*, 2014, **31**, 1946-1957.
69. E. Lu, N. Rodríguez-Hornedo and R. Suryanarayanan, *CrystEngComm*, 2008, **10**, 665.
70. Z. Zhou, H. Chan, H. Sung, H. Tong and Y. Zheng, *Pharm Res*, 2016, **epub ahead of print**, 1-10.
71. A. Manin, A. Voronin, K. Drozd, N. Manin, A. Bauer-Brandl and G. Perlovich, *European J. Pharm. Sci.*, 2014, **65**, 56-64.
72. D. Berry, C. Seaton, W. Clegg, R. Harrington, S. Coles, P. Horton, M. Hursthouse, R. Storey, W. Jones, T. Friščić and N. Blagden, *Cryst. Growth Des.*, 2008, **8**, 1697-1712.
73. H. Lin, G. Zhang and S. Lin, *J Therm Anal Calorim*, 2014, **120**, 679-687.
74. A. Ainouz, J. Authelin, P. Billot and H. Lieberman, Int. J. Pharm., 2009, **374**, 82-89.
75. K. Yamamoto, S. Tsutsumi and Y. Ikeda, Int. J. Pharm., 2012, **437**, 162-171.
76. C. Loschen and A. Klamt, *J Pharm Pharmacol*, 2015, **67**, 803-811.
77. Hanson, *Hanson solubility handbook 56*, 2016, 2342, 234.
78. M. Mohammad, A. Alhalaweh and S. Velaga, *Int. J. Pharm.*, 2011, **407**, 63-71.
79. S. Fukte, M. Wagh and S. Rawat, *International Journal of Pharmacy and Pharmaceutical Sciences.* 2014, **6**, 9-14.
80. M. Oliveira, M. Peterson and D. Klein, Cryst. Growth Des, 2008, **8**, 4487-4493.
81. S. Cherukuvada and A. Nangia, ChemInform, 2014, **45**, no.
82. N. Madusanka, M. Eddleston, M. Arhangelskis and W. Jones, Acta Crystallogr., Sect. B: Struct. Sci, 2014, **70**, 72-80.
83. T. Ueto, N. Takata, N. Muroyama, A. Nedu, A. Sasaki, S. Tanida and K. Terada, Cryst. Growth Des, 2012, **12**, 485-494.
84. S. Aitipamula, P. Chow and R. Tan, CrystEngComm, 2014, **16**, 3451-3465.
85. M. Eddleston, S. Sivachelvam and W. Jones, CrystEngComm, 2013, **1**5, 175-181.
86. M. Maniruzzaman, J. Boateng, M. Snowden and D. Douroumis, *A Review of Hot-Melt Extrusion: Process Technology to Pharmaceutical Products*, 2012, **2012**, doi:10.5402/2012/436763
87. Ghebre-Sellassie and C. Martin, *Pharmaceutical extrusion technology*, M. Dekker, New York, 2003.
88. G. Andrews, D. Jones, O. Diak, C. McCoy, A. Watts and J. McGinity, *Eur. J. Pharm. Biopharm.*, 2008, **69**, 264-273.
89. M. StankoviÄ‡, H. Frijlink and W. Hinrichs, *Drug Discov Today*, 2015, **20**, 812-823.
90. M. Maniruzzaman, J. Boateng, B. Chowdhry, M. Snowden and D. Douroumis, *Drug Dev. Ind. Pharm.* , 2014, **40**, 145-156.
91. H. Moradiya, M. Islam, G. Woollam, I. Slipper, S. Halsey, M. Snowden and D. Douroumis, *Cryst. Growth Des.*, 2014, **14**, 189-198.
92. M. Crowley, F. Zhang, M. Repka, S. Thumma, S. Upadhye,

S. Kumar Battu, J. McGinity and C. Martin, *Drug Dev. Ind. Pharm.* , 2007, **33**, 909-926.
93. A. Goyanes, P. Robles Martinez, A. Buanz, A. Basit and S. Gaisford, *Int. J. Pharm.*, 2015, **494**, 657-663.
94. M. Maniruzzaman, J. Boateng, M. Bonnefille, A. Aranyos, J. Mitchell and D. Douroumis, *Eur. J. Pharm. Biopharm.*, 2012, **80**, 433-442.
95. M. Repka, N. Langley and J. DiNunzio, *Melt extrusion, Materials, Technology and Drug Product Design*, springer, New York, USA, 2011
96. J. Breitenbach, *Eur. J. Pharm. Biopharm.*, 2002, **54**, 107-117.
97. M. Repka, S. Battu, S. Upadhye, S. Thumma, M. Crowley, F. Zhang, C. Martin and J. McGinity, *Drug Dev. Ind. Pharm.* , 2007, **33**, 1043-1057.
98. R. Dhumal, A. Kelly, P. York, P. Coates and A. Paradkar, *Pharm Res*, 2010, **27**, 2725-2733.
99. D. Douroumis, *Hot-melt extrusion*, Wiley, Chichester, West Sussex, UK, 2012.
100. R. Jani and D. Patel, *Asian J. Pharm. Sci.*, 2015, **10**, 292-305.
101. D. Markl, P. Wahl, J. Menezes, D. Koller, B. Kavsek, K. Francois, E. Roblegg and J. Khinast, AAPS PharmSciTech, 2013, **14**, 1034-1044.
102. Islam, N. Scoutaris, M. Maniruzzaman, H. Moradiya, S. Halsey, M. Bradley, B. Chowdhry, M. Snowden and D. Douroumis, Eur. J. Pharm. Biopharm., 2015, **96**, 106-116.
103. H. Moradiya, M. Islam, S. Halsey, M. Maniruzzaman, B. Chowdhry, M. Snowden and D. Douroumis, *CrystEngComm*, 2014, **16**, 3573.
104. A. Lawal and D. Kalyon, *Polym. Eng. Sci.*, 1995, **35**, 1325-1338.
105. M. Maniruzzaman, A. Nair, N. Scoutaris, M. Bradley, M. Snowden and D. Douroumis, *Int. J. Pharm.*, 2015, **496**, 42-51.
106. C. Medina, D. Daurio, K. Nagapudi and F. Alvarez-Nunez, J. Pharm. Sci., 2010, **99**, 1693-1696.
107. R. Dhumal, A. Kelly, P. York, P. Coates and A. Paradkar, *Pharm Res*, 2010, 27, 2725-2733.
108. D. Daurio, C. Medina, R. Saw, K. Nagapudi and F. Alvarez-Núñez, Pharmaceutics, 2011, 3, 582-600.
109. A. Jayasankar, A. Somwangthanaroj, Z. Shao and N. Rodríguez-Hornedo, *Pharm Res*, 2006, **23**, 2381-2392.
110. P. Grobelny, A. Mukherjee and G. Desiraju, CrystEngComm, 2011, **13**, 4358.
111. X. Liu, M. Lu, Z. Guo, L. Huang, X. Feng and C. Wu, *Pharm Res*, 2011, **29**, 806-817.
112. S. Childs, P. Wood, N. Rodríguez-Hornedo, L. Reddy and K. Hardcastle, *Cryst. Growth Des.* , 2009**, 9**, 1869-1888.
113. K. Boksa, A. Otte and R. Pinal, *J. Pharm. Sci.*, 2014, **103**, 2904-2910.
114. D. Daurio, K. Nagapudi, L. Li, P. Quan and F. Nunez, *Faraday Discuss.*, 2014, **170**, 235-249.
115. T. Friščić and W. Jones, *Cryst. Growth Des.*, 2009, **9**, 1621-1637.
116. A. Patil, D. Curtin and I. Paul, *J. Am. Chem. Soc.*, 1984, **106**, 348-353.
117. A. Trask, N. Shan, W. Motherwell, W. Jones, S. Feng, R. Tan and K. Carpenter, *J. Chem. Soc., Chem. Commun.*, 2005, 880.
118. S. Aitipamula, P. Chow and R. Tan, *CrystEngComm*, 2009, **11**, 889.
119. S. Karki, T. Friščić and W. Jones, CrystEngComm, 2009, **11**, 470-481.
120. P. Vishweshwar, A. Nangia and V. Lynch, *CrystEngComm*, 2003, **5**, 164.
121. S. Karki, T. Friščić and W. Jones and W. Motherwell, *Mol. Pharmaceutics*, 2007, **4**, 347-354.
122. S. Rehder, M. Klukkert, K. Löbmann, C. Strachan, A. Sakmann, K. Gordon, T. Rades and C. Leopold, Pharmaceutics, 2011, **3**, 706-722.
123. M. Viertelhaus, R. Hilfiker, F. Blatter and M. Neuburger, *Cryst. Growth Des.* , 2009, **9**, 2220-2228.
124. S. Basavoju, D. Boström and S. Velaga, Pharm Res, 2007, **25**, 530-541.
125. R. Chiarella, R. Davey and M. Peterson, Cryst. Growth Des., 2007, 7, 1223-1226.
126. A. Almarsson, M. Peterson and M. Zaworotko, *Pharm Pat Anal*, 2012, **1**, 313-327.
127. J. Stevens, S. Byard and S. Schroeder, *J. Pharm. Sci.*, 2010, **99**, 4453-4457.
128. M. Khan, V. Enkelmann and G. Brunklaus, *J. Am. Chem. Soc.*, 2010, **132**, 5254-5263.
129. S. Karki, T. Friščić, L. Fábián and W. Jones, CrystEngComm, 2010, **12**, 4038.
130. Reflection paper on the use of cocrsytals of active substances in medicinal products, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/07/WC500189927.pdf, accessed on February 1st, 2016.
131. C. Kulkarni, C. Wood, A. Kelly, T. Gough, N. Blagden and A. Paradkar, Cryst. Growth Des, 2015, **15**, 5648-5651.
132. N. Blagden, S. Coles and D. Berry, CrystEngComm, 2014, **16**, 5753-5761.
133. The Cambridge Structural Database, C. R. Groom, I. J. Bruno, M. P. Lightfoot and S. C. Ward, Acta Cryst. (2016). B72, 171-179. F. H. Allen, Acta Cryst., B58, 380-388, 2002. DOI: 10.1107/S2052520616003954
134. J. Liebeschuetz, J. Cole and O. Korb, J. Comput.-Aided Mol. Des, 2012, **26**, 737-748.
135. J. McKenzie, N. Feeder and C. Hunter, CrystEngComm, 2016, **18**, 394-397.
136. D. Hasa, G. Schneider Rauber, D. Voinovich and W. Jones, Angewandte Chemie, 2015, **127**, 7479-7483.
137. L. Saerens, D. Ghanam, C. Raemdonck, K. Francois, J. Manz, R. Kruger, S. Kruger, C. Vervaet, J. Remon and T. De Beer, Eur. J. Pharm. Biopharm, 2014, **87**, 606-615.
138. D. Treffer, P. Wahl, T. Hormann, D. Markl, S. Schrank, I. Jones, P. Cruise, R. Murb, G. Koscher, E. Roblegg and J. Khinast Int. J. Pharm, 2014, **466**, 181-189.