Available online at www.sciencedirect.com
ScienceDirect
Advanced Drug Delivery Reviews 59 (2007) 617–630
Advanced DRUG DELIVERY Reviews
www.elsevier.com/locate/addr

Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates☆

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Received 16 April 2007; accepted 10 May 2007
Available online 29 May 2007

Abstract

The increasing prevalence of poorly soluble drugs in development provides notable risk of new products demonstrating low and erratic bioavailabilty with consequences for safety and efficacy, particularly for drugs delivered by the oral route of administration. Although numerous strategies exist for enhancing the bioavailability of drugs with low aqueous solubility, the success of these approaches is not yet able to be guaranteed and is greatly dependent on the physical and chemical nature of the molecules being developed. Crystal engineering offers a number of routes to improved solubility and dissolution rate, which can be adopted through an in-depth knowledge of crystallisation processes and the molecular properties of active pharmaceutical ingredients. This article covers the concept and theory of crystal engineering and discusses the potential benefits, disadvantages and methods of preparation of co-crystals, metastable polymorphs, high-energy amorphous forms and ultrafine particles. Also considered within this review is the influence of crystallisation conditions on crystal habit and particle morphology with potential implications for dissolution and oral absorption.

Keywords: Crystal engineering; Crystallisation; Supramolecular chemistry; Polymorphism; Co-crystals; Solubility; Dissolution rate

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Drug solubility: How to measure it, how to improve it".

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doi:10.1016/j.addr.2007.05.011

1. Introduction

Drug molecules with limited aqueous solubility are becoming increasingly prevalent in the research and development portfolios of discovery focussed pharmaceutical companies. Molecules of this type can provide a number of challenges in pharmaceutical development and may potentially lead to slow dissolution in biological fluids, insufficient and inconsistent systemic exposure and consequent sub-optimal efficacy in patients, particularly when delivered via the oral route of administration. Advances in the pharmaceutical sciences have led to the establishment of a number of approaches for addressing the issues of low aqueous solubility. These strategies for improving and maximizing dissolution rate include micronisation to produce increased surface area for dissolution [1], the use of salt forms with enhanced dissolution profiles [2], solubilisation of drugs in co-solvents [3] and micellar solutions [4], complexation with cyclodextrins [5] and the use of lipidic systems for the delivery of lipophilic drugs [6]. Although these techniques have been shown to be effective at enhancing oral bioavailability, the success of these approaches is dependent at times on the specific physicochemical nature of the molecules being studied. Solubilisation technologies such as micellar systems are reliant on the acceptable solubility and compatibility of therapeutic molecules in a limited range of pharmaceutically acceptable excipients, whilst the increasing number of weakly ionisable and neutral molecules entering development constrains the opportunities for salt formation as a method of improving dissolution rate. Furthermore, whilst micronisation increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility. Often for drugs with very low aqueous solubility, the achieved increase in dissolution rate is insufficient to provide adequate enhancement of bioavailability [7]. The potential for increased Van der Waals interactions and electrostatic attraction between ultrafine particles can also act to reduce the effective surface area for dissolution and therefore limit improvements in bioavailability.

Crystal engineering approaches, which can potentially be applied to a wide range of crystalline materials, offer an alternative and potentially fruitful method for improving the solubility, dissolution rate and subsequent bioavailability of poorly soluble drugs. The ability to engineer materials with suitable dissolution characteristics, whilst maintaining suitable physical and chemical stability provides a strong driver for the utilisation of new and existing crystal engineering approaches to drug delivery system design. The challenges of low aqueous solubility provide an ideal situation for the application of crystal engineering techniques for improving bioavailability, whilst also developing stable and robust pharmaceutical products. This article therefore considers the potential utility of crystal engineering as an approach for designing efficacious dosage forms for poorly soluble drugs and reviews the theory, applications, benefits and drawbacks of strategies of this type.

Crystal engineering in the context of this review is taken as the design of molecular solids in the broadest sense with the aim of tailoring specific physical or chemical properties. The subject of the review is therefore to present those diverse aspects of crystal engineering which may be used to manipulate the solubility and/or dissolution rate of the parent molecular components in the crystalline state. At the centre of these available approaches is the need to change surface and molecular assembly in equilibrium with a solution. Consequently, this review covers the possible ways this may be achieved from recent developments in the study of molecular solids and reviews topical issues such as habit modification, polymorphism, solvation, co-crystal formation and surface modification. Particular attention will be paid to the area of co-crystallisation, which is an emerging area of strategic importance to the pharmaceutical sector.

The review introduces aspects of the fundamental concepts of crystallisation and describes the principles of crystal engineering which are typically used to control crystal size, shape and crystalline form. Although the primary focus considers the crystalline state, some reference will also be made to the utility of amorphous materials, with a brief summary of their use in enhancing drug dissolution and bioavailability. Also included are details of new and established methods, which enable precise control of crystallite size and shape and hence enable notable improvements in the dissolution rate of hydrophobic active pharmaceutical ingredients (APIs).

2. Crystal engineering in drug development

Crystal engineering has been described as the ‘exploitation of noncovalent interactions between molecular or ionic components for the rational design of solid-state structures that might exhibit interesting electrical, magnetic, and optical properties’. It is also recognised that it ‘is becoming increasingly evident that the specificity, directionality, and predictability of intermolecular hydrogen bonds can be utilized to assemble supramolecular structures of, at the very least, controlled dimensionality’ [8].

Supramolecular chemistry has grown around Lehn’s analogy that ‘supermolecules are to molecules and the intermolecular bond, what molecules are to atoms and the covalent bond’ [9]. If molecules are built by connecting atoms with covalent bonds, solid-state supermolecules (crystals) are built by connecting molecules with intermolecular interactions. The fundamentals of crystal engineering were described in detail under the term ‘molecular engineering’ by von Hippel in 1962 [10]. Modern

crystal engineering initially began as a method for understanding the regioselectivity and product distribution in solid-state molecular reactions, termed topochemistry [11].

This field has developed rapidly, particularly with the arrival of modern crystallographic techniques such as four circle diffractometers in the early 1970's followed by the introduction of area detector technology. Crystal engineering now encompasses many aspects of solid-state intermolecular interactions, structure prediction, control and rationalisation, as well as the synthesis of novel molecular building blocks and crystalline materials, and may be broken down into the components of analysis and synthesis [12].

Within the notion of a crystal as a supramolecular entity lies certain key ideas central to the activity of crystal engineering. These are the nature of the crystallisation process at a molecular level, crystal packing, molecular interaction and directed molecular recognition, which will all be explored to some extent in this review and which should provide some understanding of crystal engineering approaches as a means of addressing the challenges of low aqueous solubility.

3. The crystallisation process

Crystallisation is concerned with the evolution from solution or melt of the crystalline state. Within this area key issues include the formation of crystal nuclei, the influence of crystallisation conditions, and the overlap between the concepts of the growth unit, and an understanding of how the overall shape of a crystal evolves. It is within the notion of the growth unit that a distinct link with the supramolecular concept of a synthon is achieved. The term 'synthon' was originally introduced to describe synthetic organic structural features. The term 'supramolecular synthon' introduced by Desiraju [13] is defined as: 'structural units within supermolecules which can be formed and/or assembled by known conceivable synthetic operations involving intermolecular interaction'. Supramolecular synthons are spatial arrangements of intermolecular interactions; the overall goal of crystal engineering is therefore to recognise and design synthons that are robust enough to be interchanged between network structures. This ensures generality ultimately leading to the predictability of one-, two- and three-dimensional patterns formed by intermolecular interactions. The Cambridge Structural Database [14] may be utilised to identify stable hydrogen bonding motifs [15] with the ambition that the most robust motifs will remain intact across a family of related structures.

Carboxylic acids and amides contain functional groups that are self-complementary and capable of forming supramolecular homosynthons, but they are also complementary with each other and can interact through formation of a supramolecular heterosynthon (Fig. 1). This motif has been studied for some time in the context of crystal engineering [16,17] and the interaction of carboxylic acids with heterocyclic bases is perhaps the most widely studied type of synthon [18–30].

3.1. Supra molecular processes in crystal growth

Nucleation and the growth of crystals have been widely reviewed in the literature [31]. Nucleation is a molecular assembly process, where a critical number of molecules are needed to achieve the phase change from melt or solution into a crystal. The driving force for achieving a critical point of molecular assembly is linked to the free energy diagram of the process. For solution-based crystallisations, which are predominantly used in processing APIs, the free energy diagram required is linked to the solubility behaviour of the material in a chosen solvent. It is the magnitude of difference in solubility experienced by the molecules that are crystallising from totally solubilised state; at a specified composition and temperature. The larger the differential between solubilised state and the equilibrium state, the greater the supersaturation. The resulting growth of a crystal is also then dependent on the solubility behaviour and any competing nucleation which may also be taking place because of the degree of supersaturation achieved. It is therefore this phase changing process that distinguishes crystallisation from dissolution.

3.2. Crystal growth, crystal shape and the influence of habit modification

Once nucleation has been achieved, crystal growth dominates and is the process, which leads to the evolution of embryonic crystals into a crystal form of defined size and shape. The key drivers with regard to the shape of the growing crystal are related to the crystal lattice of the molecular solids and the effects of the choice of solvent and additives on the process of crystal growth. As such, crystal growth is a layer by layer process, with the evolution of the layers being defined by the crystal packing of the unit cell. The unit cell in turn describes the critical elements of how a specific molecular species has assembled in a crystalline state in three dimensions. It is the

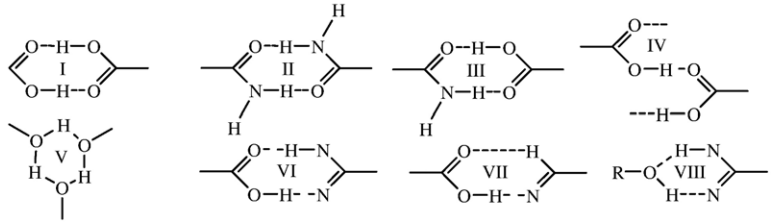

Fig. 1. Representative supramolecular synthons; I and II: homosynthons exhibited by carboxylic acid and amide dimers, III: heterosynthon exhibited by acid-amide dimers, IV: head-to-tail chains formed from carboxylic acids, V: six membered intramolecular hydrogen bond ring formed in preference to intermolecular hydrogen bonds (Hydrogen Bonding Rules), VI: robust synthon with strong N–H…O and O–H…N interactions, VII: less favoured synthon with one weak C–H…O and one strong hydrogen bond, VIII: weak synthon observed in co-crystals with diols.

strength of the intermolecular interaction defined within the unit cell which, at the first level, determines which layers dominate the crystal growth process.

It is the case that edges or corners of a crystal are related to layers of molecules which are accompanied by dominant and directional intermolecular interaction, whereas the layer-by-layer growth associated with a crystal face is related to intermolecular interactions that are less energetic in nature. A solvent or additive molecule which is able to compete for a site at an incoming point associated with the layer-by-layer growth process would be capable of disrupting the magnitude of the intermolecular interactions present between growth layers. This may then lead to a different ranking of strength of interaction between growth layers, which would manifest itself in a change in overall morphology of the crystal.

Another factor is the effect of solvent or additive molecules on the growth mechanism, particularly when solubility is affected. As solubility defines supersaturation, any change in supersaturation can cause the growth mechanism to move from screw dislocation to surface nucleation and eventually to continuous growth. This change in growth behaviour has previously been discussed in the work of Burton–Cabbera [32] and Human [33]. Predicting the transition of the growth process from one of continuous growth to one of spiral growth requires details of surface diffusion, collision and exchange processes at the growth interface.

Pioneering work at the Weisman Institute laid the foundation of the layer-by- layer growth process in terms of lock and key concepts applied to morphology, chiral resolution and polymorph isolation [34]. One example which highlights this approach is the selective inhibition of prochiral faces, (*viz* when a pair of faces are described by lattice planes that are mirror images of each other) for glycine by chiral additives, such as *L*- or *R*-serine [34]. Here, the solution was doped with either the *L*- or *R*-form of the amino acid serine. Both forms of the amino acid cause glycine crystal to grow as a pyramid, instead of growing as the usual bipyramid. This can occur because glycine possesses a prochiral axis along [010]. This prochiral axis arises as the glycine molecules form two antipolar sets within the structure (*viz* the relative mirror orientation of the molecule within prochiral lattices gives rise to alternating pairs of molecules throughout the structure) and lie perpendicular to the orientation of prochiral lattice planes. The habit modification was rationalised in terms of the *R*-serine being specific for the (010) face only and the *L*-serine being specific for the (0–10) face only.

The overall habit arises as the antipolar set typifies the plane intersecting the bipyramid, and each component of the antipolar set characterises one of the respective top faces of the bipyramid.

3.2.1. Influence of crystal habit on dissolution

It has been shown that an in-depth understanding of the crystallisation process can be applied to confer habit modification in crystalline materials. It is also known through studies of crystallisation and comminution that exposure of different crystal faces determines the nature of those faces [35], which in turn will influence the wettability and subsequent dissolution of an API.

A number of examples in the literature demonstrate the effects of changing crystal morphology on *in vitro* dissolution rate, with potential for improving bioavailability. The habit modification of dipyridamole by crystallisation using different solvents, additives and crystallisation conditions has been reported [36]. The dissolution rate of rod shaped particles crystallised from benzene was notably more rapid than for rectangular needle shaped crystals produced using methanol. In studies of phenytoin, the morphology of crystals produced under similar conditions following recrystallisation from ethanol and acetone was shown to be needle-like and rhombic respectively [37]. This change in habit was ascribed to stronger interaction of acetone with the hydroxyl groups of phenytoin, due to its relatively high polarizability. Although there were some differences in dissolution rate observed between crystalline powders of different morphology, these differences were predominantly attributed to changes in surface area rather than improvements in the wetting of more polar surface moieties. Chow et al. [38] however, when correcting for the contribution of surface area, have suggested that the crystal habit of doped crystals had a notable role to play in the enhancement of intrinsic dissolution rate of phenytoin due to an increased abundance of polar groups.

Although showing potential as a crystal engineering approach to dissolution rate enhancement, there are only a limited number of examples reported where the approach of habit modification has resulted in notable enhancement of systemic exposure in human subjects or in suitable animal models. These increases in dissolution appear to be derived from a combination of changes to crystal habit, size and even polymorphic form. Further exploration of this field is therefore required to fully establish this approach as an effective means of intentionally augmenting the bioavailability of poorly soluble drugs.

3.2.2. Methodologies for the controlled crystallisation of active pharmaceutical ingredients

Consideration of the Noyes–Whitney dissolution model (Eq. (1)) shows that drug diffusivity, solubility in the gastrointestinal contents, the surface area of the solid wetted by luminal fluids and gastrointestinal (GI) hydrodynamics all play a role in determining *in vivo* dissolution rate and consequently the rate and extent of drug absorption [39].

$$\mathrm{DR} = dX/dt = \frac{A*D}{h}(C_s - X_d/V) \quad (1)$$

where DR is the dissolution rate, A is the surface area available for dissolution, D is the diffusion coefficient of the drug, h is the thickness of the boundary layer adjacent to the dissolving drug surface, C_s is the saturation solubility of the drug, X_d is the amount of drug dissolved at time t and V is the volume of dissolution media.

The surface area of drug available for dissolution is dependent on the particle size of the API and its ability to be wetted by luminal fluids. This particle size, which is critical to drug dissolution rate, is dependent on the conditions of crystallisation or on methods of comminution such as impact milling and fluid energy milling. Although important for the

production of powders for drug administration, comminution techniques can produce particles which are highly heterogeneous, charged and cohesive, with the potential to cause problems in downstream processing and product performance [40,41]. Manufacturers of pharmaceutical dosage forms have therefore considered using methods for the controlled crystallisation of drugs to produce high purity powders with well defined particle size distribution. In particular, there has been notable interest in producing crystalline particles in the submicron size range to provide marked increases in surface area to enhance drug dissolution and bioavailability. Müller et al. have reviewed the benefits of nanoparticles and nanosuspensions on saturation solubility and dissolution velocity and described laboratory scale approaches to their production [7]. Hu et al. have discussed a number of technologies for achieving submicron sizes for therapeutic agents [42] which includes reference to supercritical fluid methodologies. This review also contains discussion of cryogenic spray processes which have a tendency to produce amorphous materials, whilst, Maheshwari et al. [43] and Paradkar et al. [44] have discussed the emerging technology of melt sonocrystallisation, which uses ultrasonic energy to produce porous fast dissolving particles for hydrophobic drug molecules.

The use of supercritical fluids in the production of micron and sub-micron particles has been considered and evaluated over the last decade. This is exemplified by the development of the solution enhanced dispersion by supercritical fluids (SEDS™) methodology by Hannah and York during the mid 90s [45]. The use of a coaxial nozzle in this technique enables the drug, which is dissolved in an organic solvent, to interact and mix with the anti-solvent, supercritical fluid CO_2 prior to transfer into the particle formation vessel via a restricted orifice. The high velocity fluid creates high frictional surface forces causing the solution to disintegrate into droplets. This has enabled the preparation of ultrafine particles for a number of materials using the SEDS™ process [46]. In addition, the Rapid Expansion of Supercritical Solutions (RESS) method has been shown to have promise and potential for improving the bioavailability of poorly soluble drugs [47,48]. The RESS-process uses the high solvating power of supercritical fluids [49] to dissolve drugs which are poorly soluble in aqueous and conventional organic solvents. After loading the supercritical fluid with the solute an extremely fast phase change from the supercritical to the gas-like state takes place during the expansion in the supersonic freejet, leading to high supersaturation and subsequently to particle formation. Since the solvent is a dilute gas after expansion, the RESS-process offers a highly pure final product [50]. Türk et al. demonstrated that particles of the poorly soluble anti-fungal griseofulvin of less than 300 nm could be produced from a supercritical solution of the drug in trifluoromethane by controlling pre-expansion temperature and pressure [47,48]. Dissolution experiments undertaken in simulated intestinal fluid (pH 7.4) showed notable improvements in dissolution rate of the RESS produced material when compared to a conventionally milled sample. No *in vivo* evaluation of its performance has however been reported to date.

Other articles demonstrating the potential dissolution benefits of ultrafine particulate drugs produced using the RESS methodology include reports on nifedipine [51], lidocaine [52] and ibuprofen [53], which show some improvements in dissolution when compared to milled and unprocessed materials. Direct comparisons with conventionally micronised drug have, however, not been reported.

Perrut et al. [54] have also reported the use of alternative supercritical fluid based methods for the production of ultrafine particles. These studies have included the investigation of the supercritical anti-solvent (SAS) and the gas-saturated solutions/suspensions (PGSS) processes. In the SAS method, a solution of the drug in an organic solvent is contacted with a supercritical solvent that causes precipitation of solid by the anti-solvent effect with the organic solvent being eventually entrained by the supercritical fluid. Copper-indomethacin particles with 90% of material having a diameter less than 10 μm have been produced by the anti-solvent approach as reported by Warwick et al. [55] and Foster et al. [53]. These particles were shown to demonstrate an 8-fold increase in dissolution rate in water compared with original form of the compound.

In the PGSS process, the API is melted in the presence of a compressed gas that dissolves in the liquid phase, which is then pulverized towards a low pressure vessel. This leads to the precipitation of solid particle. Nifedipine processed by the PGSS method using supercritical CO_2 was shown to provide notable increases in dissolution rate when compared to unprocessed materials [56,57]. However, as with the examples provided for the anti-solvent approach, the *in vitro* performance of these particles has been compared only to unprocessed material and not to conventionally micronised drug or to substances formulated using alternative bioenhancement strategies. Although the benefits to material properties and surface area are clear, further work is required to explore comprehensively these techniques as a robust and reliable means of enhancing dissolution and bioavailability.

3.3. Crystal growth and polymorph selection

The impact of crystal form on pharmaceutical development has been the subject of numerous reviews with Singhal and Curatolo providing one of the most recent articles in 2004 [58]. In particular, the influence of crystalline modification on drug dissolution and bioavailability has been considered for a whole library of molecules and was first highlighted for the well-known example of chloramphenicol palmitate in the late 1960s, in which metastable polymorph B was shown to provide notably greater absorption in humans than polymorph A [59]. It was suggested that where large free energy differences between polymorphs exist, the greater solubility of the metastable form could be exploited to enhance absorption and bioavailability.

A route to polymorph selection and stabilization is to employ additives or solvents (impurities), which have the ability to inhibit or interfere with the fastest growth directions of a stable polymorph over that of metastable form exhibited by the system. Such studies highlight the subtle role that growth conditions play in crystallisation, and have direct ramifications

for the supramolecular chemist engaged in crystal engineering. As such, this work highlights the effect kinetics and growth conditions may have on the durability of a synthon to generate a particular architecture. This arises since such systems are subject to the issue of the growth of one form over another, which is described by Ostwald's rule of stages [60], which states 'when a change in phase occurs, the transformation proceeds not directly to the most stable phase but to the next stable'. Consequently, for solution crystallisation, polymorphism adds a kinetic dimension to crystal growth. Whereby, the kinetics requires that the transformation of one phase to another in solution is dependent on the dissolution of the metastable phase, [61], (as stated in Eq. (2)), driving the growth of the stable phase, as defined by Eq. (3).

$$G_{\mathrm{I}} = -k_{\mathrm{d}}\left(\sigma - \sigma_{(i-ii)}\right) \tag{2}$$

$$G_{\mathrm{II}} = k_{\mathrm{g}}\left(\sigma_{(i-ii)}\right) \tag{3}$$

where G=growth rate, σ=supersaturation, and the subscripts indicate phases I or II, g — growth, d — dissolution.

Such a description of the transformation kinetics suggests that the stabilisation of metastable form using an impurity would require the impurity to influence the growth kinetics of the stable phase. In the case of glutamic acid, the impurity used was trimesic acid, as this impurity is a conformational mimic of glutamic acid in the stable form. Consequently, an impurity of this type will disrupt the growth of the stable form of glutamic acid *via* disruption of the fastest growth direction, and this arises because the trimesic acid has a larger molecular volume than the host site within the fastest growth direction, thus disrupting the next incoming layer.

Polymorph selection attempts to combine aspects of packing landscapes, thermodynamics, kinetics and concepts of supramolecular assembly in order to develop a strategy for the exploration and control of polymorphism through solvent choice. At the one level an understanding of the solubility behaviour of one polymorph versus another is required. This is then used in combination with a specific cooling curve and prudent choice of solvent to produce the target polymorph. At another level, a series of solvents with distinctive classes of solvation behaviour are employed in an automated screen. Up to now, this approach has met with a mixed level of success. Starting with systems with well-documented crystal structures and phase behaviour, the results show that a high level of manipulation and control is possible, however as this work has moved into the area of molecules for which little or no previous data existed the outcome is less clear [62]. This research requires an examination of how structure prediction might be included into the polymorph selection process [63,64]. More specifically these studies [63,64] were undertaken to explore the concept of directing a specific assembly, and to gain an insight into the possibilities and limitations of this type of approach. A certain of level of control has been achieved to the extent that patterns of assembly in the crystal packing identified during the simulation and selection process were observed in the experimental crystal structures obtained with crystals grown in selected solvents [65]. The failings encountered indicate that some additional critical steps are required when undertaking crystal prediction. These include principal growth unit identification and subsequent use of mixed growth units, the recognition of the role solvent molecules contribute to viable growth units, and the role kinetics has on understanding the "Aufbau" principle [66] of how molecules pack into crystals. The key challenges that remain include the need to understand better how to engineer selection by eliminating areas of packing space by improving the identification of key parameters which influence the population of building units and thus the kinetics of the resulting nucleation and crystal growth process [67]. This in turn would reduce the landscape of possible polymorphs or alter the ranking of polymorphs. In this way it may be able to improve the success rate or selectively engineer a structure [68].

Current understanding makes it possible to reduce the predicted packing landscape, as simulations undertaken may only be concerned with what is identified as a viable molecular aggregate once a ranking scheme has been applied [69] or a refinement of the intermolecular interactions is achieved through higher level calculation [70].

Overall, it is anticipated that these concepts would find use in polymorph screening initiatives, particularly when high throughput identification of polymorphs also utilises simulated structures.

3.4. The influence of crystal form on drug solubility, dissolution and bioavailability

Although the utilisation of metastable polymorphs offers a route to improved dissolution and oral bioavailability, concerns still exist with respect to conversion of these materials to more stable crystalline forms during processing and storage. Nonetheless, there have been numerous reports demonstrating the influence of polymorphic and crystalline form on dissolution rate and/or oral bioavailability. These have included discussions on the crystalline forms of phenobarbital [71], spironolactone [72] and carbamazepine [73] in which metastable crystalline forms have provided enhanced dissolution behaviour. Pandit et al. [74] also showed differences in dissolution rate, area under the plasma concentration time curve (AUC) and maximum plasma concentration ($C_{\max}$) for two different polymorphs of phenylbutazone in beagle dogs, whilst Singhal and Curatolo reviewed a number of examples showing differences in pharmacokinetic profiles in human subjects relating to batch to batch variations in the polymorphic forms of carbamazepine and oxytetracycline [58].

In all of the examples discussed, although polymorphic forms of APIs with increased dissolution were shown to provide improvements in *in vitro and in vivo* performance, it is believed that equilibrium solubility is not the important factor for the enhancement of oral absorption, particularly when physical forms are unstable in the aqueous environment of the gastrointestinal (GI) tract.

Although when considered in isolation, differences in solubility between polymorphs are believed to have relevance for

improvements to dissolution rate, absorption and bioavailability, equilibrium solubility becomes irrelevant if interconversion to the most stable form occurs in the GI lumen. Instead, intrinsic dissolution rate or kinetic solubility over a 4–6 h period may be more relevant parameters to consider when assessing the potential for improved oral absorption [58]. It should be noted however, that intrinsic dissolution rate still does not indicate the likely magnitude of solid form transformation occurring during oral administration or provide information on the precipitation of less soluble forms and so reliable predictions of the rate and extent of absorption are not possible directly from these measurements. This concept is particularly important, when considering the performance of crystalline materials with propensity to form hydrates, which for some compounds [73] will typically lead to precipitation from solution during GI transit.

Kobayashi et al. [73] showed that the initial dissolution rate of carbamazepine dihydrate in simulated fluids (pH 1.2) was notably slower than the anhydrous forms (forms I and III). During these experiments, the initial dissolution rate of the metastable polymorph (Form III) was greatest, although this form was shown to convert to the dihydrate more rapidly than the stable form (Form I), resulting in subsequent reductions in dissolution rate at later time points of the profile. Similar to the findings of dissolution studies, the AUC measured following administration of carbamazepine to beagle dogs at a dose of 200 mg was lowest for the dihydrate. The metastable form however gave lower AUC than the stable form, which is consistent with probable conversion to the dihydrate *in situ*. Tian et al. [75] have however shown that conversion to the hydrated form can be inhibited by the presence of excipients such as polyethylene glycol (PEG) and hydroxypropylmethylcellulose (HPMC). Strategies such as these may therefore provide value when considering the use of metastable polymorphs to enhance dissolution in the GI tract.

In general, the range of solubility differences between different polymorphs is typically only 2–3 fold due to relatively small differences in free energy [58]. It is this relatively small difference in solubility, coupled with the potential for interconversion to more stable and less soluble forms in the GI lumen, which limits the potential benefits of using metastable crystalline forms for enhancing oral absorption and bioavailability. Researchers have therefore considered the use of stabilized high-energy amorphous systems, typically in the form of solid dispersions, which can demonstrate orders of magnitude increases in solubility and provide markedly increased dissolution and absorption [76]. These amorphous systems, however, provide major challenges to achieving adequate physical and chemical stability and appropriate processing properties [77].

3.5. High energetic materials — the amorphous form

Yu has previously reviewed the subject of amorphous pharmaceutical solids and has given details of preparation methods, characterization techniques and methods of stabilization [77]. There have been numerous reports on the character and properties of amorphous pharmaceutical materials and it is therefore not the intention to review the literature further in this article. However, although philosophically and theoretically outside the scope of crystal engineering, it is important to note the benefits of amorphous materials on dissolution rate and subsequent oral absorption. As the number of poorly soluble drugs entering pharmaceutical development increases, there has been a marked interest in the use and stabilization of amorphous systems by many pharmaceutical companies. This has been exemplified by the plethora of technology patent applications filed in the last 10 years. Binary amorphous dispersions of poorly, water soluble drugs with polymeric excipients have received much interest as a route to improving drug solubility, dissolution and thus bioavailability. However, as the amorphous phase is metastable compared to the crystalline state, there is some risk that phase transformation will occur upon storage, limiting their use in pharmaceutical dosage forms.

No doubt drug molecules which are not easily crystallised have been presented as the amorphous form in marketed pharmaceutical products. However, poorly soluble drugs, which have intentionally been developed as amorphous forms to enhance oral bioavailability, have often been formulated as solid dispersions. The generic term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method [78]. The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs was first recognised in 1961 [79].

In the preparation of solid dispersions, drugs with a poor ability to form the glassy state, and which demonstrate notable propensity to crystallise, have generally been made amorphous by deliberately preventing crystallisation. Recent additional preparation techniques have included rapid precipitation by freeze drying [80] and spray drying [81] and using supercritical fluids [82], often in the presence of intrinsically amorphous hydrophilic polymers and also using methods such as melt extrusion [83]. In these systems, the drug substance is either molecularly dispersed within the polymer matrix to form a solid solution or distributed as amorphous drug domains and nanoparticulates.

Under appropriate conditions of temperature and humidity, amorphous materials can crystallise when sufficient molecular mobility exists. Vitrification strategies for stabilization used in approaches such as solid dispersions, tend to rely on the immobilization of drug molecules in rigid glasses of the inert carrier. Increasing the glass transition temperature (Tg) of the carrier or using additional additives with high Tg, reduces the potential for crystallisation of the drug substance [77], although storage conditions and packaging components may still need to be controlled to prevent conversion to crystalline forms. The selective hydrogen bonding of amorphous drugs with stabilizing excipients, may also have a role to play in maintaining the amorphous state [77]. Although physical and chemical stability is a considerable concern for amorphous systems, if these high-energy forms can be prevented from crystallisation during their intended storage life period, this approach to bioavailability enhancement can be a powerful approach to improving dissolution in GI fluids.

There are a number of literature reports which have demonstrated the improved *in vitro and in vivo* performance of drugs delivered in the amorphous form. The AUC and C_{max} of glibenclamide delivered in the form of a solid dispersion with PEG6000, was shown to be greater than those measured for the commercially available tablets when given to 6 healthy male volunteers [84]. Studies of an amorphous solid dispersion of ritonovir, a Biopharmaceutics Classification System (BCS) Class IV compound with low solubility and permeability, showed a 10-fold increase in intrinsic dissolution rate when compared to its crystalline counterpart. In beagle dogs, this improved dissolution behaviour resulted in significant improvements in AUC and C_{max} for the amorphous dispersion produced using a solvent evaporation and fusion method [85]. Similarly, the solid dispersion of the novel dual 5-lipoxygenase/cyclooxygenase inhibitor ER-34122, also prepared by solvent evaporation, gave an improved *in vitro* dissolution rate compared to the crystalline drug substance [76]. When orally administered to beagle dogs, the amorphous ER-34122 showed an approximate 100-fold increase in both C_{max} and AUC compared with the pure drug. It is therefore clear that highly energetic amorphous forms have marked potential for improving the bioavailability of poorly soluble drugs. Continued attention must however be given to the development of convenient methods for the preparation and stabilization of these inherently unstable systems.

3.6. The co-crystal route

This article has covered a number of crystal engineering routes, which have demonstrated potential to improve drug solubility and dissolution. Each of those discussed, however, has indicated a number of drawbacks which might limit their applicability. An alternative approach available for the enhancement of drug solubility, dissolution and bioavailability is through the application of crystal engineering of co-crystals, historically referred to as molecular complexes. Pharmaceutical co-crystallisation is emerging as an attractive alternative to polymorphs, salts and solvates in the modification of an active pharmaceutical ingredient (API) during dosage form design. The physicochemical properties of the API and the bulk material properties can be modified, whilst maintaining the intrinsic activity of the drug molecule. The intellectual property implications of creating co-crystals are also highly relevant.

This co-crystal approach [86] requires the development of a supramolecular library of co-crystallising agents [87]. Within the library a hierarchy of guest functional groups is classified according to a specific contribution to a crystal packing arrangement, which is dependent on the functionalities contained on the host molecule. These are derived from examining structure property relationships present in classes of known crystal structures contained in the Cambridge Structural Database (CSD) [88].

A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces [89]. There has however been much debate about the use of the term co-crystal. Desiraju challenges the use of co-crystal and favours the term molecular complex to describe multi-component crystals having specific non-covalent interactions between the distinct molecules [90]. In contrast Dunitz defends the use of co-crystal as encompassing molecular compounds, molecular complexes, solvates, inclusion compounds, channel compounds, clathrates and possibly other types of multi-component crystals [91]. He argues that the terms molecular complex, molecular compound and intermolecular complex have typically been used in a very broad sense and should not be used exclusively to describe the crystalline state but should also be used to describe the solid, liquid and even gaseous states in which the constituent molecules are considered to be more strongly associated than in a simple mixture.

It is within the definition of molecular complexes that the literature provides examples of co-crystals of active pharmaceutical ingredients, and an early report is for the sulphamides, [92]. However, as with the conflicting views on definition of co-crystals, there remains some disagreement whether to include solvates in the set of co-crystals. Morissette et al. [93] claim that co-crystals (of drugs and drug candidates) are part of the broader family of multi-component crystal systems that includes salts, solvates, clathrates, inclusion crystals and hydrates, and that the primary difference between solvates and co-crystals is the physical state of the individual components [93]. If one component is liquid at room temperature then the crystals are designated solvates, whereas if both components are solids at room temperature then the crystals are designated as co-crystals. Solvates are commonplace because they occur as a serendipitous result of crystallisation from solution [94] and have the potential to enhance drug dissolution rate, as shown for the solvated forms of spiranolactone [72]. Solvated crystals however are often unstable, leading to desolvation during storage and such solvent loss may lead to the amorphous phase crystallising into less soluble forms. Solvent levels in solvated crystals are also often at concentrations that are not acceptable to regulatory authorities and which may also have toxicological consequences. Co-crystals, however, tend to be a product of more rational design and are more stable, particularly as the co-crystallising agents are solids at room temperature. As with other crystalline systems, polymorphic co-crystals are not uncommon. At least 20 have been reported to date, including caffeine and glutaric acid polymorphic co-crystals [95].

Further insight into the terminology of solvates was provided by Rodriguez-Spong et al. [96]. They described solvates as a special type of multi-component solid that can be classified depending on the molecular network of the solvent molecules. If the solvent is an integral part of the network structure and forms at least a two-component crystal, then it may be termed a co-crystal. If the solvent does not participate directly in the network itself, as in open framework structures (i.e. the main function of the guest molecule is a cavity filler in a host molecule assembly having a channel, layer or 3D framework structure), then it is termed a clathrate (inclusion complex).

Whilst co-crystals are defined by a single phase (miscible) multi-component system in the crystalline state, in the amorphous state they have been referred to as molecular dispersions [97,98] with interactions between the components distinguishing them from solid dispersions. Co-crystals are not

classified as solid dispersions; nevertheless solid dispersions may occur when attempting to prepare co-crystals from solution.

3.6.1. General design strategies for co-crystallisation

Co-crystal screening is a process similar to salt screening and is particularly suited to high-throughput technologies [93]. Once an API has been selected for co-crystallisation studies, a pharmaceutically acceptable, non-toxic co-crystallising agent(s) should be chosen so as to result in a pharmaceutically acceptable product. This limits the co-crystallising agent to those that have been approved for consumption by humans, for example pharmaceutical excipients and compounds classified as generally recognised as safe (GRAS) for use as food additives (as classified by the U.S. Department of Health and Human Services).

The Food Additives Status List provides data on limitations to use and permitted tolerances for each additive. For complete information on a substance's use and limitations, reference to the specific regulation for each substance is advised. Most GRAS substances have no quantitative restrictions as to their levels in food products, although their use must conform to good manufacturing practices. Although GRAS substances are generally recognised as safe in foods, their levels and use can be restricted in pharmaceutical products. Where there is no precedent of pharmaceutical use and where the intended additive has no pharmacopoeial monograph, GRAS status does not guarantee its use as co-crystal forming agent. Even where precedents exist, the inclusion of additives is restricted to levels demonstrated to be safe in existing pharmaceutical products. For example the maximum additive level of malic acid (which has been co-crystallised with the anti-fungal drug itraconazole) in hard candy is <7% [99].

A number of co-crystals have been formed with co-crystallising agents classified as GRAS. For a viable application in drug development, the required therapeutic level, however, needs to be balanced with the level of active drug and therefore, unless the resulting stoichiometric amount of co-crystal agent is less than the permitted additive level, their pharmaceutical applications will not be realised.

Co-crystallisation between two APIs has also been proposed as a basis for both compounds to be pharmaceutically acceptable. This may require the use of sub-therapeutic amounts of drug substances such as aspirin or acetaminophen [94], or the APIs to have similar levels of therapeutic active concentration.

The majority of co-crystallisation research has rarely involved using pharmaceutically acceptable co-crystallising agents and conditions. The formation of paracetamol adducts with hydrogen-bond acceptors has been reported [102]. However the co-crystallisation agents used were not GRAS substances, and piperazine dihydrochloride and morpholine as the salt(s) of one or more fatty acids, are only permitted as food additives at the relevant level [100].

3.6.2. Co-crystal design

One approach to co-crystal design has been based on consideration of pK_a [99]. Although salts and co-crystals may be distinguished by an absence of proton transfer in co-crystals, it can be argued that rather than a distinct difference between them, there is in fact a scale which progresses from strong ionised salts, to weak salts and through to neutral hydrogen-bonding structures. Solution chemistry demonstrates that a pK_a difference of at least two units (between an acid and a base) is required to form a salt that is stable in water [101].

Co-crystallisation of *cis*-itraconazole with a series of 1,4-dicarboxylic acids capable of extended (anti-) conformations was observed [99]. Interaction between succinic acid and the strongest base position of itraconazole however was not present in the co-crystal structure. Co-crystals could not be formed from maleic acid with Z regiochemistry about the C═C bond (with pK_{a1} = 1.9), or from 1,3- or 1,5-dicarboxylic acids. Therefore in this case structural fit appears to be far more important than acid-base strength complimentarity for successful co-crystallisation.

In the study of the relative humidity stability of a series of caffeine/carboxylic acid co-crystals [102] it was found that the strongest acid guest molecule (oxalic acid) produced the most stable caffeine co-crystal, whilst the weakest acid (glutaric acid) produced the least stable cocrystal. However, a polymorph of the glutaric acid/caffeine co-crystal displayed intermediate stability; therefore pK_a alone must not be the only factor dictating co-crystal stability.

The use of hydrogen bonding rules, synthons and graph sets may assist in the design and analysis of co-crystal systems. In general though, prediction of whether co-crystallisation will occur is not yet possible and must, at present, be answered empirically.

Co-crystal formation may be rationalised by consideration of the hydrogen bond donors and acceptors of the materials that are to be co-crystallised and how they might interact. Following the extensive examination of preferential packing preferences and hydrogen-bond patterns in a number of organic crystals, Etter and co-workers proposed the following guidelines to facilitate the deliberate design of hydrogen bonded solids [18].

1. All good proton donors and acceptors are used in hydrogen bonding.
2. Six-membered ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds.
3. The best proton donor and acceptor remaining after intramolecular hydrogen-bond formation will form intermolecular hydrogen bonds to one another (but not all acceptors will necessarily interact with donors).

These observations help to address the issue of competing hydrogen bond assemblies observed when using a particular co-crystallising agent.

3.6.3. Methods of preparation of co-crystals

Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together. Sublimation, growth from the melt, and slurry preparation have also been reported [103].

Co-crystal formation described in the literature indicates the notoriously difficult situation these systems present with regard

to preparation — it has been known to take 6 months to prepare a single co-crystal of suitable quality for single X-ray diffraction analysis [104] and of the 10 new co-crystals of carbamazepine reported, approximately 50 co-crystal agents were used, giving a success rate of 20% [105]. This is partly because such a heteromeric system will only form if the non-covalent forces between two (or more) molecules are stronger than between the molecules in the corresponding homomeric crystals. Design strategies for co-crystal formation are still being researched and the mechanism of formation is far from being understood [86].

For solution co-crystallisation, the two components must have similar solubility; otherwise the least soluble component will precipitate out exclusively. However similar solubility alone will not guarantee success. It has been suggested that it may be useful to consider polymorphic compounds which exist in more than one crystalline form as co-crystallising components. If a molecular compound exists in several polymorphic forms it has demonstrated a structural flexibility and is not locked into a single type of crystalline lattice or packing mode. Thus, the chance of bringing such a molecule into a different packing arrangement in coexistence with another molecule is increased [89]. Clearly polymorphism alone does not guarantee the functionality of a compound to act as a co-crystallising agent, whilst the ability of a molecule to participate in intermolecular interactions obviously plays a critical role [86].

When preparing co-crystals, the product obtained from grinding is generally consistent with that obtained from solution [106]. This may indicate that hydrogen-bond connectivity patterns are not idiosyncratic or determined by non-specific and unmanageable solvent effects or crystallisation conditions. Nevertheless there are exceptions. Whilst many co-crystal materials can be prepared from both solution growth and solid-state grinding, some can only be obtained by solid-state grinding [107]. An example is that in the co-crystallisation of 2,4,6-trinitrobenzoic acid and indole-3-acetic acid, different crystal forms were obtained from solution compared with grinding [107].

Failure to form co-crystals by grinding may be due to an inability to generate suitable co-crystal arrangements rather than due to the stability of the initial phases. When co-crystal formation has been successful from solution, but not from grinding, solvent inclusion in stabilising the supramolecular structure may be a factor [108]. Although co-crystal formation by solid-state grinding has been established for some time and a late 19th century report is often cited as the earliest reference to such a procedure [109], the recent technique of adding small amounts of solvent during the grinding process has been shown to enhance the kinetics and facilitate co-crystal formation and has lead to increased interest of solid-state grinding as a method of co-crystal preparation [110].

In the case of cyclohexane-1,3*cis*,5*cis*-tricarboxylic acid with bipyridine, previously found to co-crystallise from MeOH solutions, when an equimolar mixture was ground for 60 min, only partial conversion occurred, whereas the addition of ~0.05 ml of MeOH to the milling process accelerated co-crystallisation such that complete conversion was achieved in 20 min. When a solvent in which neither starting component was soluble was added to the milling process (cyclohexane), kinetic enhancement was not observed and reaction did not occur even after 90 min grinding. This kinetic enhancement was rationalised by the additional degrees of orientational and conformational freedom open to the molecules at the various interfaces with increased opportunities for molecular collisions. Another possibility is the formation of minute co-crystal seeds forming within the solvent, thereby increasing the rate of co-crystallisation. An important factor to consider in the solvent choice should therefore be that it is able to partially dissolve the original components. The use of this solvent mediated solid-state grinding as a pre-test for whether co-crystals can be synthesised from solutions was proposed by the authors [110]. The application of this method as an attractive eco-friendly (green chemistry) route for co-crystallisation without the use of large amounts of solvents was also anticipated.

3.6.4. Phase diagrams for co-crystallisation

An important aspect of understanding co-crystal formation from solution is the tertiary phase diagram. A limited number of experimentally derived phase diagrams exist [92,103,111–114]. Of those reported the trends which emerge are summarised below in Schemes 1 and 2 (Fig. 2), where *A*=component+solution (S), *B*=*A*+co-crystal, and I or II=co-crystal phases+solution.

Depending on the difference in solubility of the co-crystal, the extent of mixed regions of concomitant co-crystal, components, and metastable phase formation were found to be dependent on the difference in solubility of the co-crystal components. For a system with two co-crystal phases, Scheme 1 the phase diagram

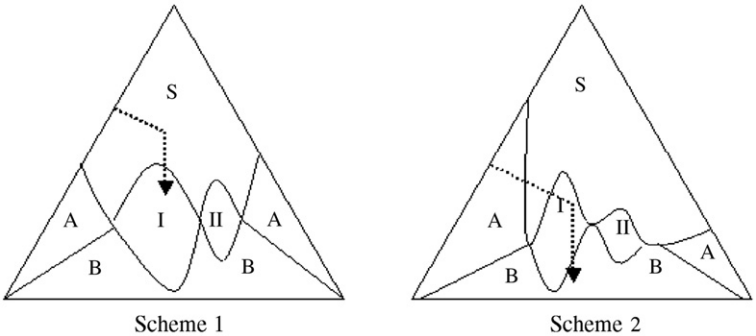

Fig. 2. Tertiary phase diagrams for co-crystallisation.

represents the situation where the components have similar solubility in solvent 1, while Scheme 2 represents the situation where the components have different solubilities.

The arrow in each diagram highlights the typical route of crystallisation. For Scheme 1 with equivalent solubility of components, the crystallisation route at equimolar components leads to form co-crystal I, (1:1 ratio in the solid). For non-equivalent solubility of the components, Scheme 2 applies and this leads to the possibility of the individual components crystallising together with the co-crystal; as the crystallisation route may pass through regions A, B and I. For Scheme 2, if a kinetic process exists this would account for the possible initial formation of phase II over phase I, as well as the observation of new polymorphs of the components and outcomes observed in grinding experiments.

3.6.5. Physicochemical properties of co-crystals and dissolution rate enhancement

At present, other details regarding the physicochemical properties of co-crystals have not been reported. In particular there have been no studies published to date regarding the chemical and physical stability of these systems. Although it is assumed that the intrinsic activity of the API would remain unchanged, there is no published evidence to support this fact to date.

Supramolecular complexes of carboxylic acid APIs with dipyridyl co-crystallising agents have been prepared — $(\text{ibuprofen})_2$(4,4′-bipyridine), A, $(\text{flurbiprofen})_2$(4,4′-bipyridine), B, $(\text{flurbiprofen})_2$(1,2-bis(4-pyridyl)ethylene), C, and $(\text{aspirin})_2$ (4,4′-bipyridine), D, and their melting points determined [115]. The melting points of A–C were higher than their pure individual components, whereas the melting point of D (which exhibited dramatically different molecular packing compared to the other co-crystals) had a much lower melting point than its pure components. The melting points of thirteen carbamazepine co-crystals have also been reported, with only two having a melting point higher than pure carbamazepine, as part of a study into the crystal engineering of pharmaceutical phases [105]. However, many of these compounds would not be classified as co-crystals using the definition adopted in this work, as the co-crystallising agents are liquids at room temperature e.g. acetone and acetic acid. In addition, only three of the co-crystallising agents are classified as GRAS (saccharin, nicotinamide and acetic acid) limiting the pharmaceutical applications of this work.

The stability of a solid drug material with respect to atmospheric moisture is important to the pharmaceutical industry, due to the practical implications of hydrate formation upon processing, formulation, storage and packaging [116]. The relative humidity stability of a series of caffeine/dicarboxylic acid co-crystals has been examined with respect to the pure crystalline anhydrous caffeine [102]. No co-crystal hydrates were observed, and the co-crystals that were unstable with respect to relative humidity tended to dissociate to the crystalline starting materials. A humidity induced polymorphic transformation was also observed. The caffeine/oxalic acid co-crystal was stable at all measured relative humidities, displaying better stability than the anhydrous caffeine.

The dissolution of co-crystals of itraconazole, a triazole drug, with succinic acid, malic acid and tartaric acid, was compared to that of the pure crystalline and amorphous drug by Remenar et al. [99]. The authors found that in general, the co-crystals behaved in a similar manner to the amorphous form compared with the crystalline drug in achieving and sustaining from 4- to 20-fold higher concentrations on dissolution testing. The practical implications of this finding are important, as the ability to form and sustain a supersaturated solution can have a dramatic impact on drug absorption and bioavailability [117]. Furthermore, McNamara et al. [114] have shown that a co-crystal of a development candidate API formed with glutaric acid increased its aqueous dissolution rate by 18 times over that of the homomeric crystalline form. Studies in beagle dogs showed that the co-crystal form also gave notably increased plasma AUC compared to the parent crystal form. Nevertheless, whilst the research of Remenar et al. [99] and McNamara et al. [114] have shown the potential benefits of co-crystal formation on drug dissolution and bioavailability, this embryonic area of pharmaceutical research is still relatively unexplored and requires further study before co-crystals can be considered to be a reliable toolbox technology for the enhancement of oral drug absorption.

4. Conclusions

It is clear that the crystal and particle engineering strategies described in this article have notable potential to strengthen the available methods for addressing problems of low aqueous solubility of drug substances. These methods are applicable not only to molecules of a specific physical and chemical nature, but to a wide range of crystalline materials, although a comprehensive knowledge of drugs at the molecular level is required to determine the appropriate approach to improving solubility and dissolution rate.

The controlled production of ultrafine particles, particularly at sizes below 1 μm is becoming a favoured strategy for the pharmaceutical industry. In addition to the established comminution methods available to the formulator, new and emerging methods of controlled crystallisation provide an opportunity to produce highly pure crystalline drugs with narrow size distribution and desirable morphology. Although there are few disclosed examples of success in human subjects, there is sufficient evidence to demonstrate the potential benefits on dissolution in aqueous environments.

The formation of molecular complexes and co-crystals is becoming increasingly important as an alternative to salt formation, particularly for neutral compounds or those having weakly ionizable groups. Despite lack of precedence in marketed products and concerns about the safety and toxicity of co-crystal forming agents, there is growing interest and activity in this area, which aims to increase the understanding of co-crystal formation and methods of preparation.

Although, some recent developments in crystal and particle engineering have been included within this review, consideration of established approaches such as the use of high-energy amorphous and metastable crystalline forms is still widespread.

In particular substantial advancements in methods for isolating metastable crystalline have been achieved since the early days of chloramphenicol palmitate, whilst a greater understanding of the production and stabilisation of amorphous forms is also leading to a renaissance in their use.

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