Pharmaceutical solvates, hydrates and amorphous forms: A special emphasis on cocrystals☆

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Abstract

Active pharmaceutical ingredients (APIs) may exist in various solid forms, which can lead to differences in the intermolecular interactions, affecting the internal energy and enthalpy, and the degree of disorder, affecting the entropy. Differences in solid forms often lead to differences in thermodynamic parameters and physicochemical properties for example solubility, dissolution rate, stability and mechanical properties of APIs and excipients. Hence, solid forms of APIs play a vital role in drug discovery and development in the context of optimization of bioavailability, filing intellectual property rights and developing suitable manufacturing methods. In this review, the fundamental characteristics and trends observed for pharmaceutical hydrates, solvates and amorphous forms are presented, with special emphasis, due to their relative abundance, on pharmaceutical hydrates with single and two-component (i.e. cocrystal) host molecules.

Keywords:
Hydrates
Solvates
Amorphous form
Cocrystal
Hydrated cocrystal
Solvated cocrystal
Solid dispersion
Water cluster
Solid state characterization
Tendency for hydrate formation

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1. Introduction

Pharmaceutical solids are classified as thermodynamically stable crystalline and unstable amorphous forms. A crystalline solid can be characterized by the presence of three-dimensional long-range order. However, amorphous solids are characterized by the presence of random atomic structure and a short range order of molecules. These molecules are randomly oriented in different directions and show different conformational states. The lack of three-dimensional long-range order is commonly manifested as a diffuse X-ray diffraction pattern and lack of melting endotherm [1]. A mesophase material (e.g. liquid crystals) is described as having intermediate symmetry, while the amorphous state shows no symmetry (Fig. 1) [2,3]. Such differences in the range of melting endotherms [1] can be decribed as having intermediate symmetry, while the amorphous state shows no symmetry (Fig. 1) [2,3]. Such differences in the range of melting endotherms [1].

The behavior of amorphous materials can be elucidated by changes in thermodynamic parameters (free volume, enthalpy and entropy) with a variation in temperature. Amorphous solids are further characterized by the absence of distinctive melting points. When the molar volume or heat content of an amorphous sample is plotted against temperature (Fig. 1), the behavior of amorphous materials can be elucidated by changes in thermodynamic parameters (free volume, enthalpy and entropy) with a variation in temperature. Amorphous solids are further characterized by the absence of distinctive melting points. When the molar volume or heat content of an amorphous sample is plotted against temperature (Fig. 1), the term glass forming ability (GFA) is defined as the ability to form a glassy state during cooling or vice versa during heating, and is manifested as a step change in heat content (Fig. 1) [2,3]. Such differences in the range of melting endotherms [1] can be described as having intermediate symmetry, while the amorphous state shows no symmetry (Fig. 1) [2,3].

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Acknowledgements

References
solid form of APIs should be selected for first-time-in-man/human formulation development prior to scale-up and clinical trials [13].

With a view to achieving a common consensus, industrial and academic researchers from crystal engineering and pharmaceutical sciences recently suggested a comprehensive classification scheme for the solid forms of APIs and multicomponent systems (Fig. 2) [18].

Hydrates and solvates are thus multicomponent crystalline solid molecular adducts containing both the host molecule (API or excipient) and guest molecule (water (hydrate) or other solvents (solvate)) incorporated in the crystal lattice structure, commonly known as pseudopolymorphic forms.

Water and other solvent molecules often form H bonds and coordinate covalent bonds in a crystal lattice with APIs or excipients. Most small molecular weight APIs and excipients tend to form solvates and hydrates readily due to their small molecular size. Water molecules have both hydrogen bond donor and acceptor atoms, which can form intermolecular hydrogen bonding with host molecules. As a result, hydrates are the most common type of solvated organic compounds [19]. The presence of water molecules affects the level of intermolecular interactions (internal energy and enthalpy) and the degree of crystalline disorder (entropy). Hence, it impacts the free energy, thermodynamic parameters, solubility, dissolution rate, solid state stability, and bioavailability of hydrated APIs. Mechanical properties and deformation mechanisms such as tableting, grinding/milling can also vary among different solid forms (Table 1) [20].

Crystallization is governed by thermodynamic and kinetic conditions, where it is generally advocated to use slow cooling to generate relatively pure stable polymorphic forms [36]. Altered kinetic conditions (e.g. rapid cooling) may lead to a mixture of stable form(s), metastable polymorphs and/or amorphous forms.

2.1. Principles of water and solvent associations

There are various means by which solvent can be associated with crystalline solids: adsorption on a solid surface, adsorption and absorption into disordered regions and crystal defects, the physical inclusion of liquid during crystal growth, and solvent associated as part of crystal packing (solvates or hydrates) (Fig. 3) [37]. Adsorbed water can exist as a monomer, dimer, multimer, 2D bilayers, 3D clusters and diverse ice structures [38]. Amorphous solids and disordered systems (metastable regions) usually have higher volumes and weaker intermolecular interactions, hence solvent association is relatively higher than for crystalline forms [37].

Solvents can lead to problems in organic compounds by inducing disorder in the crystal structure, leading to the formation of relatively metastable systems. However, solvent molecules in the crystal lattice can also create strong interactions and hydrogen bonding with APIs and other solvent molecules to form flexible clusters, which can improve the stability of metastable solid forms [39–43]. Solvent molecules may also play a role of space fillers in the crystal lattice without forming strong interactions with host molecules [44,45].

Water is one of the most abundant molecules on the earth’s surface and in the atmosphere [46]. It has a unique chemistry compared to other organic solvents, consisting of two positive and two negative regions of charge [20,47]. Generally, electrostatic forces, electrostatic charge transfer, covalent bonds, dispersion forces and exchange repulsions are the main components of hydrogen bonds [47]. Hence, a water molecule can form a coordinate covalent bond, a hydrogen bond or van der Waals interaction including induced dipole, dipole-dipole, and dispersion forces with API(s) or excipient(s), which is attributed to the acidic —OH fragments and the basic oxygen lone pairs [47].
compounds with proton donors moieties (R—OH, R1R2—NH), proton acceptors moieties (R—COO−, R—O−, Cl−) and other highly electron negative atoms tend to be involved in intermolecular hydrogen bonds with water molecules [20].

2.2. Tendency for hydrate formation and nature of water clusters

2.2.1. Factors affecting the tendency for hydrate formation

Based on a study conducted in 1995, ~5% of water molecules in hydrated organic compounds are without intermolecular interaction [48]. Water molecules can form tetrahedral networks due to interactions among the two hydrogens (hydrogen bond donors) and the two lone pairs of an oxygen atom (hydrogen bond acceptors) [49]. They can also form flexible hydrogen bonds with other organic compounds in disordered or ordered systems. Water molecules fill void spaces in crystal lattice structures and form intermolecular hydrogen bonds with organic compounds. The intermolecular hydrogen bonding may provide stability to the crystal lattice, improving the stability of the hydrated crystal form compared to the anhydrous crystal form [50]. There are a significant number of marketed stable hydrated forms of APIs; for example, the cardiovascular drug creatine phosphate sodium tetrahydrate (CPS·4.5H2O) [51], the beta-lactam antibiotic ampicillin trihydrate [52] and the synthetic broad spectrum cephalosporin antibiotic, cepalexin monohydrate [53].

Water molecules can exist as a cluster of multiple numbers of molecules in hydrated crystaline organic compounds. Infantes et al. presented the results of comprehensive studies, based on the Cambridge Structural Database (CSD), to identify the critical factors affecting the tendency for hydrate formation for organic crystalline compounds, and the nature of the clusters of water molecules in hydrated structures [50,54,55].

In an earlier study of 2566 hydrates from the CSD, Desiraju showed that 65% of the hydrated structures have a hydrogen bond donor–acceptor ratio of <0.5, indicating an inverse relationship between the tendency for hydrate formation and the donor-acceptor ratio of organic compounds [56]. The presence of water molecules provides additional options of hydrogen bond donors and acceptors for organic compounds with an extreme imbalance in the number of donor and acceptor groups or atoms. This enables the hydrogen donors or acceptors to be involved in intermolecular hydrogen bonding.

Infantes et al. identified the sum of the average donor and acceptor counts of the functional groups, polarity and the presence of charged atoms or groups as critical factors affecting hydrate formation in organic crystal structures (Table 2) [55]. However, this database study on 34,770 organic crystal structures showed no significant effect of the donor/acceptor ratio or the molecular weight of the organic compounds on the tendency for hydrate formation [55]. The polarity of functional groups and atoms was strongly related to the tendency for hydrate formation, where organic compounds with highly polar and charged functional groups or atoms accounted for >90% of the total hydrates from the CSD database. For example, the charged R—COO− (03) functional group of amoxicillin and R—NH2− functional group of gabapentin form strong hydrogen bonding with water molecules in the crystal structure of amoxicillin trihydrate (beta-lactam antibiotic, space group P212121, CSD refcode: AMOXCT10) (Fig. 4a) and CSD refcode: QIMKOM) (Fig. 4g), respectively. Hydrate formation can

**Table 1**

Physical properties of solid forms which have been shown to change with solid state form [13].

<table>
<thead>
<tr>
<th>Physical properties</th>
<th>Examples (*hydrate or solvate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packing properties</td>
<td>Unit cell volume (crystalline forms only) Sulfanilamide [21]</td>
</tr>
<tr>
<td></td>
<td>Density Indomethacin [22] (in most cases, stable forms have higher density and smaller unit cell volume) and sulfanilamide [21]</td>
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<tr>
<td></td>
<td>Refractive index Sulfanilamide [21]</td>
</tr>
<tr>
<td></td>
<td>Melting point Carbamazepine [23]</td>
</tr>
<tr>
<td></td>
<td>Enthalpy, entropy and free energy Most polymorphic forms</td>
</tr>
<tr>
<td></td>
<td>Solubility Carbamazepine (anhydrous form I and form II) [24] and carbamazepine (anhydrous form I and dihydrate)* [17]</td>
</tr>
<tr>
<td>Thermodynamic properties</td>
<td>Dissolution rate Anhydrous theophylline [25] and carbamazepine dihydrate* [17]</td>
</tr>
<tr>
<td></td>
<td>Rates of solid state reaction Vitamin A [26]</td>
</tr>
<tr>
<td></td>
<td>Stability (chemical and physical) Prednisolone tert-butyrate [27] and quinapril HCl [28]</td>
</tr>
<tr>
<td>Kinetic properties</td>
<td>Surface free energy Paracetamol (disparity in wetting properties of the same Miller indexed faces) [29]</td>
</tr>
<tr>
<td></td>
<td>Crystal habit Ritonavir [30]</td>
</tr>
<tr>
<td>Spectroscopic properties</td>
<td>Surface free energy transitions (far-IR or microwave spectra)<em>, vibrational transitions (Infrared (IR) and Raman spectra)</em>, rotational transitions (nuclear magnetic resonance (NMR) spectra)<em>, nuclear spin transitions (nuclear magnetic resonance (NMR) spectra)</em></td>
</tr>
<tr>
<td></td>
<td>Compaction Paracetamol [34]</td>
</tr>
<tr>
<td>Mechanical properties and processability</td>
<td>Hardness/tensile strength, compactability/tableting Paracetamol [34]</td>
</tr>
<tr>
<td></td>
<td>Flowability/blending Paracetamol [34]</td>
</tr>
</tbody>
</table>

*Example of solvates and hydrates. **Physical properties of solid forms which have been shown to change with solid state form [13].

**Fig. 3.** Schematic representation of principles of solvent associations with pharmaceutical solids [37].

also be affected by the experimental conditions (shear forces and the presence of seeds) during the crystallization process in an aqueous environment [59].

Table 2
Factors affecting hydrate formation in organic compounds (based on references [50,55,56,60] and examples from the CSD).

<table>
<thead>
<tr>
<th>Factors</th>
<th>Examples</th>
<th>References/Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>The polarity of functional groups and atoms</td>
<td>(COO(^-)) [55], R2PO2(^-), Cl(^-) and C–NH(_3)(^+) [60]</td>
<td>Compounds with charged atoms and groups or high polarity have a high tendency of forming hydrates.</td>
</tr>
<tr>
<td>Hydrogen bond donor-acceptor ratio (d/a)</td>
<td>3,5-Dinitrosalicylic acid(^+), 2, 5-nitrosaliclyic acid(^+) and 3-amino-5-nitrosalicylic acid (^+) [56]</td>
<td>Has low d/a (&lt;0.5) and crystallized as monohydrate and (^+) have high d/a crystallized as anhydrous [56]. This finding was only applicable for randomly selected samples (limitation).</td>
</tr>
<tr>
<td>The total number of hydrogen bond donor and</td>
<td>Higher number of acceptor and donor groups and atoms, and extreme imbalance between them, correlated with high tendency for hydrate formation [54]</td>
<td></td>
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<tr>
<td>acceptor groups and atoms, and the balance</td>
<td></td>
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<tr>
<td>between them</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polar surface</td>
<td>High percentage of polar surface is correlated with higher tendency for hydrate formation whereas polar volume is not critical parameter [55]</td>
<td></td>
</tr>
<tr>
<td>Unsatisfied hydrogen bond donors</td>
<td>Compounds with higher number of unsatisfied hydrogen bond donors groups and atoms have shown higher tendency for hydrate formation [60]</td>
<td></td>
</tr>
<tr>
<td>Chirality of organic compounds</td>
<td>Chiral compounds have a higher tendency for hydrate formation than achiral compounds. Enantiopure compounds have higher tendency for hydrate formation than racemic forms [60]</td>
<td></td>
</tr>
<tr>
<td>Kinetic and external factors</td>
<td>Caffeine, carbamazepine, nitrofurantoin, sulfguanidin and theophylline [59]</td>
<td>Compound-specific properties (solubility) and process parameters (the presence of seeds and extent of applied shear) [59]</td>
</tr>
</tbody>
</table>

Previous studies are either based on random sampling from the CSD database or use of a data retrieval approach with limitations. Streek et al. used an in-house software to overhaul what they considered to be...
data harvesting problems of the ConQuest program from the CSD database. They were able to extract data from the CSD database on compounds having both solvated and unsolvated forms, compounds having only solvated or unsolvated forms, crystallization solvent used, and the stereochemistry of the compounds, [60]. Streek et al. found that the number of water molecules per asymmetric unit of host molecule increases with both molecular weight and the number of hydrogen bond donor and acceptor groups. The charged function groups have a relatively high degree of prevalence in hydrated forms of organic compounds [60], which is a similar observation to that of Infantes et al. [55]. The average number of contacts was also specific to functional groups. In contrast to Desiraju's work [56], the tendency for hydrate formation was determined to be more related to the overall number of acceptor and donor groups [60]. The unsatisfied donor groups were found to be often more critical than the acceptor groups in dictating the tendency for hydrate formation [60]. The various factors which tend to affect hydrate formation in organic compounds are summarized in Table 2.

2.2.2. Water clusters in hydrated organic compounds

Water molecules can participate in intermolecular interaction with other water molecules and the host organic compound in the crystal lattice. Based on the pattern of water clusters, hydrates may be classified as follows: (1) isolated lattice site (discrete chains or rings), where water molecules are devoid of any direct hydrogen bond; (2) chain (chain or tape structures), where water molecules form a direct intermolecular hydrogen bond to create a tunnel; (3) expanded channels; (4) lattice planes; (5) dehydrated hydrates and (6) metal–ion coordinated hydrates, where water molecules directly interact with alkali and transition metals [61]. The water cluster may be part of a very complex intermolecular interaction pattern in the crystal structure, where the same water molecules can often form a number of different hydrogen bonds with the host organic compound. For instance, the water molecules in ampicillin trihydrate are part of both the acyclic discrete chain of water molecules cluster and the supramolecular heterosynthons with the carboxylic acid, the amide carbonyl and the primary amine groups of ampicillin (Fig. 4b) [50]. The hydrogen bonds are considered as an important type of intermolecular interaction in multicomponent crystalline systems, and the structures formed by those hydrogen bonds can be among the same (termed homosynthon) or different (termed heterosynthon) functional groups [62].

Infantes and Motherwell presented a comprehensive analysis of the nature of water clusters for hydrated organic compounds in the CSD using the ConQuest search program [50]. Water molecules were found to exist in diverse patterns of clusters: discrete chains, discrete rings, infinite chains in one dimension involving no rings, infinite tapes in one dimension involving rings, and infinite layers in two dimensions (Fig. 5). ~5% of the structures had a water molecule cluster which differed from the general classification and was classified as cross-linked discrete rings, unclassified structures in one dimension, unclassified structures in two dimensions, and infinite networks in three dimensions [50].

Most of the water molecule clusters (ca. 61%) in organic molecule crystals exist as acyclic discrete chains (D, Fig. 5), of which 73% of them contain two water molecules with intermolecular hydrogen bonding, as depicted in Fig. 5 as D2. The third most abundant pattern of water molecules clusters also have discrete but cyclic patterns containing three to nine water molecules (Rn, n=3 to 9, Fig. 5). The second most abundant pattern of water clusters contain infinite acyclic chains of water molecules (C, Fig. 5) where the number with the letter designation stands for the number of water molecules in a unit cell for a water cluster in a crystal lattice structure [50].

2.2.3. Water clusters and ‘structure-stability’ of hydrated cocrystals

A cocrystal can be described as a crystalline structure formed by generally two, or sometimes more, different molecular entities, present in stoichiometric ratio. Cocrystals can exist as anhydrous or hydrous solid forms that can convert to either form during dissolution, manufacturing, and storage. There is no distinction between the nature of the water cluster in hydrated cocrystals and that in hydrated organic compounds with only one type of host molecule.

In hydrated cocrystals, water molecules form intermolecular interactions with either or both components (API and co-former) of the cocrystal. Water molecules form a combination of cluster patterns in the alprazolam hemikis (succinic acid) trihydrate (Fig. 4c, CSD refcode: CAKZUL) cocrystal, where four water molecules form a discrete ring (R4) with intermolecular hydrogen bonding. A discrete ring bridges water molecules and the nitrogens of the five-member heterocyclic triazole ring of alprazolam. One more water molecule forms a discrete chain (D2) with one of the water molecules in the discrete ring (R4). This discrete chain creates strong intermolecular interactions with succinic acid and the nitrogen of the benzodiazepine ring, which acts as a linker between alprazolam and succinic acid.

Water molecules can simply be involved in intermolecular hydrogen bonding without forming any type of cluster. Water molecules obstruct the acid–amide heterosynton of temozolomide and acetic acid cocrystal to form a monohydrate (Fig. 4d) [63]. There are few studies and limited understanding of the structural factors which affect the stability of hydrated cocrystals. Clarke et al. presented a comprehensive study on 11 hydrated cocrystals with a view to understanding the interplay between structure and stability [64]. Generally, the correlation between stability (dehydration temperature) and the three structural properties of hydrogen bond donors and acceptors, nature of water cluster (tunnels or isolated) and packing efficiency (the volume fraction of atoms in crystal structure per volume of unit cell) was insignificant [64]. The water cluster pattern affected the dehydration temperature, where the tunnels hydrate tended to lose water near the boiling of water, whereas the dehydration temperature of the isolated hydrates depended on the number of strong hydrogen bonds [64].
Cocrystallisation can also decrease the tendency to hydrate formation, where the co-former can take over the role of the water molecule in the crystal structure. For instance, anhydrous caffeine has a tendency to form hydrates with varying degrees of hydration, which is attributed to a high imbalance between the number of a hydrogen bond donors (ca. zero) and acceptors (ca. six) with a hydrophilic center at the imidazole ring nitrogen [65]. Water molecules form an infinite chain and strong intermolecular interactions with the imidazole ring nitrogen (N4 or N3) (Fig. 4e). Trask et al. showed that caffeine and dicarboxylic acid co-formers, oxalic acid and malonic acid, form heteromeric synthons with a strong O—H—N (N4 or N3) and a weaker C—H—O hydrogen bond (Fig. 4f) [58]. The anhydrous caffeine-dicarboxylic acid cocrystal forms showed superior physical stability to anhydrous caffeine upon storage at higher humidity, which was attributed to the absence of a free imidazole ring nitrogen (N4 or N3) for hydrate formation in the cocrystal.

2.3. Survey of hydrated organic compounds: CSD 2016

Intermolecular interactions like hydrogen bonding are inevitable interactions between water molecules and/or water and host organic compounds. Steiner reported that, of a sample of 672 water molecules from compounds of biological origin (amino acids, alkaloids, carbohydrates, nucleosides and nucleotides, purines and pyrimidines, steroids), only 4%were the water molecules devoid of hydrogen bonding [48].

ConQuest 1.18 (CSD software, Cambridge, UK) was used to search for text entries and extract the number of hits from the CSD 2016. The search for “hydrates” resulted in 105,450 hits including organics, organometallics, small molecules, polymers, disordered and ordered systems, of which hydrated organic molecules without traces of disorder accounted for about 19% (20,249 hits). The hydrated organic molecules contain from 1/2 (hemihydrates) to 19 (nonadecahydrates) molecules of water per host organic molecule. The trends in hydrated organic molecules entry, the number of molecules in the asymmetric unit (Z prime), unit cell structure (Z) and calculated density are presented in this section for hydrated organic molecules with and without bioactivity.

Various pharmacological activities such as analgesic, antihelmintic, antimalarial and others and related keywords are stored in the “Bioactivity” field of the CSD, where ‘Drugs’ are also included in this search field. “Bioactivity” may also include biologically active compounds (e.g. insecticidal) and receptor(s) (Conquest user manual, page 184). A search of “bioactivity” generates 13,976 (1.6% of the total entries) hits out of ca. 850,000 entries in the CSD.

2.3.2. Trends in the frequency of functional groups

The polarity of functional groups or atoms had been reported to be a critical property affecting the tendency for hydrate formation in crystaline organic compounds [60]. Charged functional groups and polar surface area are often correlated with the high frequency of hydrates in the CSD database, as was comprehensively discussed in the previous sections [55]. Hydroxyl moieties also showed a clear trend, where a hydroxyl group attached to a tertiary carbon is the most common, followed by secondary and primary structures [60].

The combination of all text searches for ‘hydrate’, ‘bioactivity’ and ‘functional group’ showed that hydroxyl moieties are the most common type of functional group, followed by halogens, in hydrated organic compounds with biological activity, but there is no obvious trend in terms of frequency of occurrence of hydroxyl groups attached to primary, secondary or tertiary carbons (Fig. 7b) (CSD updated version 5.37 (May 2016)). The occurrence of charged functional groups, NH3R+ and COO−, is relatively low.

2.4. Phase transformation of hydrates and solvates

Particle engineering and solid form modification of APIs and functional excipients can occur during spray drying [68,67], crystallization [68], milling [69,70], wet extrusion, wet granulation and hot melt extrusion [71]. Multiparticulate systems and tablet dosage forms can be coated by functional excipients to modify drug release [72], to avoid chemical degradation [73] and to reduce irritation of parts of the gastrointestinal tract [74]. The use of solvent and mechanoactivation in these manufacturing processes may lead to solution and/or solid-mediated phase transformations.

The physical stability of solid phases depends on experimental and manufacturing process conditions such as temperature, pressure, and composition or the presence of a solvent, where only one solid phase has a minimum free energy in a given condition. Generally, the mechanisms of phase transformation are solid-, melt state- and solution-mediated (Table 3). Solid phases can undergo a polymorphic transformation, solvation/desolvation, crystallization of amorphous forms and vitrification during manufacturing, storage, and dissolution [75,76].

Exposure of metastable solid forms to a liquid vehicle(s), aqueous or organic solvent, may lead to solution-mediated phase transformation. An aqueous or organic solvent can dissolve traces or part of the API, which leads to the formation of a saturated solution followed by nucleation and precipitation (crystallization) to a stable form. Solution-mediated phase transformation can occur from a supersaturated solution or on the surface of a dissolving solid during dissolution, and in the course of manufacture and storage of liquid dosage forms as aqueous suspensions [77]. Phase transformation can lead to the precipitation of a less soluble and stable solid form from a metastable form [78]. Exposure to high humidity over the shelf life of the therapeutic product may also lead to the transformation of APIs and excipients to hydrated phases [20].

Cardew and Davey presented a comprehensive and detailed theory on the kinetics of solution-mediated phase transformations for both inorganic and organic compounds [36,79]. Depending on the experimental conditions, such as concentration, temperature, and pressure, precipitation from a solution with composition xA_{supersaturated} (supersaturated composition for stable phase II) may lead solution-mediated phase transformation to a thermodynamically favorable less soluble and more stable solid phase (phase II) (Fig. 9) [36]. A solution with xA concentration, which is supersaturated for both the stable and the metastable phases, can precipitate to both metastable and stable phases. According to Ostwald’s Law of Stages, nucleation, and crystal growth kinetics favor the formation of the metastable phase I at the initial stage of precipitation from solution with xA concentration, which leads to a decrease in concentration to xA. At a later stage, the concentration is supersaturated only with respect to the stable phase, leading to nucleation of this form. The relationship between dissolution and crystal growth processes governs the phase transformation from metastable to the stable phase,

where the metastable phase dissolves during crystal growth of the stable phase to maintain a saturated solution for the metastable phase. Generally, metastable solid phases have a higher solubility, which may enhance the bioavailability of the drug from the drug product. The drug release of the metastable phase (phase I) can be as high as the equilibrium solubility \( (x_i) \) during dissolution which may lead to nucleation and the crystal growth of phase II. The transformation kinetics depend on the dissolution rate of the metastable and growth rate of

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the stable phase [76]. The degree of supersaturation dictates both nucleation and crystal growth according to the simplified Cardew and Davey model. Various reviews are available on solid-state characterization techniques before and during dissolution [76,80].

Various additional factors such as specific rate constants, interfacial energies, free energies of formation, solute diffusivity and mixing intensity may also affect the crystallization kinetics during solution-mediated phase transformation. Thompson and Dixon used population balance models to simulate solution mediated phase transformation by incorporating these diverse numbers of factors. These population balance models for metastable phase transformation can simulate, not only the degree of supersaturation but also the size distribution and composition of the solid particles [81].

Solution-mediated transformation of APIs and excipients alters physicochemical properties, which may affect drug product performance. However, the Cardew and Davey model, which is based on an interplay between dissolution and growth rate, was unable to simulate anhydrate-hydrate transformation of nitrofurantoin, theophylline, caffeine, sulfaguanidine, and carbamazepine under wet granulation process conditions. In this study, Wikstrom et al. identified that solution mediated hydrate formation is compound specific and was also dictated by surface properties, seeding conditions and shear forces [59].

A dissolution-precipitation model can also be applied to forecast drug absorption from the gastrointestinal tract. Prediction of bioavailability of new chemical entities can alleviate the problem of small sample quantity during early stage drug product development. Jakubiaj et al. proposed a mechanistic dissolution-precipitation model which takes into account not only dissolution and dose-dependent precipitation but also precipitation (nucleation and growth) initiated by undissolved solids. The dissolution-precipitation model combined with a physiological model predicted the oral bioavailability of dipyrindamole, bifonazole, aripiprazole and other APIs [82]. The mechanistic model was also further applied to explain the solution-mediated polymeric transformation of piracetam, tobutamide, ritonavir and L-glutamic for diverse experimental conditions: solvent, temperature, solution concentration and total solid composition [83].

Solid-mediated phase transformation occurs in the solid state without transformation to the gaseous or liquid state. The kinetic driving forces for solid-state transformation are temperature, pressure, moisture, crystal defects, particle size distribution, and impurities [75]. Surface and bulk crystallizations dictate the overall crystallization of amorphous drugs. However, the surface crystallization growth rate is often faster than the bulk crystallization of solids in the glassy state. As a result, mechanical stresses which affect particle size distribution and surface area can lead to solid-mediated phase transformation to other solid state forms. For instance, the surface crystallization of felodipine is six times faster than the bulk of the powder [84].

Zhang et al. published a comprehensive review of manufacturing process induced phase transformation and solid state considerations during product development of solid oral dosage forms [75]. Manufacturing processes which involve mechanical stress may lead to the formation of crystal defects or amorphous material and can cause phase transformation to metastable polymorphic forms. The most commonly used manufacturing processes for oral solid dosage forms use solvents and high temperature for drying. These manufacturing processes can lead to a solution- and/or solid-mediated transformation and to solvation or desolvation of APIs or functional excipients. A comprehensive summary of manufacturing process induced phase transformation, mechanisms of the transformation and examples are presented in Table 3.

Figure 7 (a) The number of water molecules per host molecule for entries in CSD-2016 and (b) the number of functional groups in hydrated organic compound with biological activity ('BIOACTIVITY') from the CSD-2016.

2.5. Solvated and hydrated cocrystals

Pharmaceutical cocrystals have emerged in the last two decades as a new promising class of solid form in the arena of advanced drug development. Broadly speaking, a cocrystal is considered to be a multicomponent molecular crystal, which is a crystalline adduct comprising two or more chemically different components. This definition also includes solvates, hydrates, and lattice inclusion molecules [100]. Bernstein et al. observed that at least 50% of compounds, when screened thoroughly for polymorphs, show polymorphism [101]. A similar level of occurrence of polymorphism was also observed for cocrystals and slightly lower levels were observed for solvates and hydrates [101]. Cocrystal based systems were generally believed to show a lesser propensity for different polymorphic forms, solvates, and hydrates when compared to single-component crystalline systems. However, recent literature shows that cocrystals have the same propensity to form different polymorphs, solvates, and hydrates as single-component crystalline systems. Studies related to crystal form diversity in terms of polymorphs and pseudopolymorphs of the cocrystal is an increasing trend [102–105].

Pharmaceutically active molecules are considered to be a niche class of cocrystals, as most of them contain active functional groups which are involved in molecular level recognition interactions with biological receptors. These same active functional groups generally account for various conformations, crystal packings, and interaction with water/solvent molecules to form hydrates/solvates [106]. Cocrystal hydrates and solvates belong to another class of crystalline solid form, and are often found during cocrystal screening. The ability of cocrystals to form...
polymorphs and hydrates/solvates has been examined by means of their occurrence in the CSD. The number of polymorphic cocrystals and their hydrates/solvates that have been added to the CSD in recent years is larger than for single component crystals [103]. This may be due to the increasing interest in the development of cocrystals as novel entities [107].

**Fig. 8.** Calculated density (g/cm³) in a publication year, and the number of molecules per asymmetric unit (\(Z'\)) compared with the number of molecules per unit cell (\(Z\)) for hydrated organic molecules from the CSD-2016.
The probability of the two-component cocrystals forming varied and multiple hydrogen bonding motifs with different functional groups, such as carboxylic acid and hydroxyl groups, invariably leads to cocrystal polymorphism. Similarly to single component systems, in crystallization processes, the combination of structure-related factors (hydrogen bonding motifs, different donor–acceptor ratio, and variable conformations) and process-related factors (crystallization medium, temperature profile, and solubility kinetics and supersaturation level) gives rise to diverse possibilities for supramolecular transformations. These possibilities make the outcome of cocrystallization unpredictable; the final outcome can be a different polymorphic form/solvate/hydrate. This variability can be considered an adversary to crystal engineering because of the high level of unpredictability [108]. For example, Row et al. studied the polymorphs of a 1:1 GA (gallic acid)–SM (succinimide) cocrystal. Three different stoichiometry hydrates (1:1:1, 2:2:1 and 2:4:1) of the GA cocrystal. Three different stoichiometry hydrates (1:1:1, 2:2:1 and 2:4:1) of the GA–SM cocrystals were obtained concurrently with polymorph I of the 1:2 cocrystal upon crystallization of 1:1 GA–SM hydrate. These hydrates show similar supramolecular patterns, with voids filled with variable numbers of water molecules. They also found GA–SM cocrystal solvates, where 1:4-dioxane (1:1:1) and acetone (2:2:1) solvates were observed initially. Other different associated solvates like (GA–SM–tetrahydrofuran in 2:2:1 and GA–SM–ethyl acetate in 3:3:1 ratios) were also observed [108]. This shows the complexity of cocrystal related systems (Fig. 10). There are numerous reported polymorphs, solvates, and hydrates of other cocrystals which are summarized in Table 4.

### 2.6. Cocrystal polymorphs

Generally, single entity polymorphism can be classified into the categories of synthon, packing, conformational, and tautomeric polymorphism. Synthon polymorphism can be identified by the presence of different forms of the primary synthons [121]. Conformational polymorphism can be defined as molecular moieties with varied rotational degrees of freedom which embrace different conformations in the unit cell [111]. Packing polymorphism applies to similar molecular moieties packing into different periodic crystal structures [109]. Tautomeric polymorphism can be defined as the coexistence of crystallized tautomers in equilibrium conditions [119]. Cocrystals include two or more molecular entities in the single unit cell, so the classification of polymorphs in cocrystal systems should be based on conformational differences of constituents, as well as on the basis of the intermolecular interactions among the different constituent molecules. Altipamula et al. classified different types of polymorphism observed in cocrystals [107]. In the current review, cocrystal polymorphism involving APIs and co-formers is described. In addition, information about polymorphism in cocrystal hydrates and solvates in also presented.

#### 2.6.1. Synthon polymorphs

Synthon polymorphism can be identified by the presence of different forms of the primary synthons [121]. They differ in their primary hydrogen-bond motifs. A systematic methodology for designing cocrystals has introduced the theory of supramolecular synthesis, where specific intermolecular interactions are identified initially which can unfailingly bring together two different molecules, in a process parallel to organic covalent synthesis. The synthon principle of organic synthesis has been used to define supramolecular synthons which can be assembled by known intermolecular interactions. Examples of homomeric interactions, which is another name referring to homosynthons, include carboxylic acids, amides, oximes, and pyridines etc. Heterosynthons are more frequently observed in cocrystals than homosynthons. General heterosynthons that are reported repeatedly in the literature include carboxylic acid-amide, carboxylic acid-pyridine, and alcohol-pyridine. Cocrystals of carbamazepine (CBZ) with nicotinamide (NCT) and saccharin cocrystal are shown to exist as heterosynthon polymorphic forms.
Two polymorphs of CBZ-NCT cocrystals and two polymorphs of CBZ-SAC cocrystals have been observed [122]. The CBZ-SAC (form II) cocrystal represents a heterosynthons polymorph (Fig. 11a and b) [110]. These findings are important, as CBZ based cocrystals are among the most extensively researched cocrystals [110]. Polymorphs of 4-hydroxybenzoic acid (4HBA) and 4,4′-bipyridine (BP) denote a common example of synthons cocrystal polymorphs where the form I contains acid–acid dimer and hydroxyl–pyridine synthons, while form II shows acid–pyridine and hydroxyl–carbonyl synthons [121]. Dubey and Desiraju reported synthons polymorphs of the quercetin-bipyridine cocrystal system (QUE: 4BP) [111]. Molecules which have multiple H-bonding capabilities are more inclined to form synthon polymorphs. The table (Table 4) shows a few more examples of pharmaceutical cocrystal systems which demonstrate synthon polymorphism.

2.6.2. Conformational polymorphs

Conformational polymorphism can be identified by the existence of different molecular conformations in the polymorphs. This is generally observed in flexible molecules which show high degrees of torsional freedom. Specifically, low-energy conformers show more susceptibility for conformational polymorphism. The existence of a conformational polymorphism in pharmaceutical materials has been credited to their flexible molecules with high degrees of torsional freedom. Pharmaceutical molecules which are flexible conformationally may possess a higher chance to show polymorphism, as the energies required for rotational bonds (single) are similar to the lattice energy gap between polymorphs. In terms of cocrystals, various studied cocrystal polymorphs show different conformers of the cocrystal constituents and, hence, can be categorized as conformational cocrystal polymorphs. Boldyreva et al. have reported glycine cocrystals with the carboxylic acid glutaric acid as the co-former [113]. This glycine-glutaric acid cocrystal has shown a structural phase transition on increasing pressure. This phase transition is related to a change in the glutaric acid conformation. The data obtained from the glycine–glutaric acid cocrystals study suggest that if a crystal contains conformationally flexible molecules, like glutaric acid, and rigid components, like glycine, then the pressure-induced phase transition depends on the conformational changes of the flexible component [113].

Lian et al. have studied the conformational polymorphism of nicotinamide cocrystals and observed that nicotinamide is a conformationally flexible molecule and forms cocrystals with various lower energy co-formers as well as with high energy co-formers. The nicotinamide cocrystals with high energy co-formers have comparable formation volume and energies as those cocrystals with the low energy co-formers. This versatile nature of nicotinamide to show conformational flexibility may be responsible for its ability to form numerous cocrystals [114]. Terada et al. observed four conformational polymorphs of furosemide—nicotinamide 1:1 cocrystal [112]. A thermodynamic stability study of

<table>
<thead>
<tr>
<th>Pharmaceutical substance [references]</th>
<th>Co-formers (Number) and type of polymorphs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil (5-FU) [109]</td>
<td>4-hydroxybenzoic acid (2) Synthon</td>
</tr>
<tr>
<td>Carbamazepine [110]</td>
<td>Nicotinamide (2) Synthon</td>
</tr>
<tr>
<td>Carbamazepine [110]</td>
<td>Saccharin (2) Synthon</td>
</tr>
<tr>
<td>Ethenzamide [102]</td>
<td>Saccharin (2) Synthon</td>
</tr>
<tr>
<td>Quercetin [111]</td>
<td>4,4′-Bipyridine (4) Synthon</td>
</tr>
<tr>
<td>Furosemide [112]</td>
<td>Nicotinamide (4) Conformational</td>
</tr>
<tr>
<td>Glycine [113]</td>
<td>Glutaric acid (2) Conformational</td>
</tr>
<tr>
<td>Nicotinamide [114]</td>
<td>R-mandelic acid (2) Conformational</td>
</tr>
<tr>
<td>Felodipine [115]</td>
<td>4,4′-Bipyridine (2) Conformational</td>
</tr>
<tr>
<td>Caffeine [116]</td>
<td>Anthranilic acid (2) Packing</td>
</tr>
<tr>
<td>Celecoxib [117]</td>
<td>1,2-Di(4-pyridyl) ethylene (DPE) (2) Packing</td>
</tr>
<tr>
<td>Celecoxib [117]</td>
<td>1,2-Bis(4-pyridyl)ethane (BPE) (2) Packing</td>
</tr>
<tr>
<td>Salicylic acid [118]</td>
<td>N,N′-diacyltylperazine (2) Packing</td>
</tr>
<tr>
<td>Piroxicam [119]</td>
<td>4-Hydroxybenzoic acid (2) Tautomer</td>
</tr>
<tr>
<td>Triclabendazole [120]</td>
<td>3,5-Dihydroxybenzoic acid (DHBA), 3,5-dinitrobenzoic acid (DNBA), oxalic acid, succinic acid, fumaric acid, 3,5-diminitrosalicic acid (DNSA), maleic acid, adipic acid, glutaric acid, malonic acid (MA), salicylic acid (SA), and aspirin. (2) Tautomer</td>
</tr>
</tbody>
</table>

Fig. 10. Various possible outcomes of co-crystals.

these polymorphs was performed by slurry conversion experiments, and stability was determined to be in the order: I > III > II > V > IV.

2.6.3. Packing polymorphs

Packing polymorphism applies to similar molecular moieties packing into different overall 3-D crystal packing [109]. Different packing of constituent molecules with similar conformations can be referred to as packing polymorphism. It is sometimes confusing to differentiate between conformational polymorphism and packing polymorphism as most of the polymorphs show some differences in conformation. Although there is no clear difference between packing polymorphs and other reported types of polymorphs, the earlier is more common for very rigid molecules and molecules with fragile conformational flexibility. Skovsgaard and Bond studied cocrystal polymorphism [118]. They observed cocrystals between benzoic acid: diaza-bicyclo-octane (2:1), and benzoic acid: aminopyridine (2:1). They used solution and solvent-drop grinding as cocrystallizing methods and observed that the polymorphs obtained by the grinding method had a higher packing coefficient than the polymorphs obtained by the solution method [118]. In the same study, they observed that the crystal packing of forms I and form II in a salicylic acid and N, N′-diacetyl piperazine cocrystal (2:1) showed significant differences despite the similar hydrogen bonding pattern in both polymorphs (Fig. 11c and d). They observed a layered pattern in form I, however, this layered pattern was absent in form II [118].

2.6.4. Tautomeric polymorphs

When different tautomers of an organic compound crystallize and co-exist in equilibrium in multiple crystal forms, they can be termed as tautomeric polymorphs [119]. Generally, tautomeric polymorphism occurs when the isomers exist in the dynamic equilibrium with each other. The tautomers that interconvert in solution are considered to be the same chemical compound, and therefore the crystal forms that comprise these tautomers can be categorized as polymorphs. A cocrystal of the nonsteroidal anti-inflammatory drugs (NSAIDs), piroxicam, with 4-hydroxybenzoic acid (4HBA) demonstrates tautomeric polymorphism. One of the polymorphs shows the piroxicam molecule as the zwitterionic form, whereas the other contains it as the non-ionized form [119]. Desiraju et al. carried out several cocrystallization experiments on triclabendazole with several co-formers which included dihydroxybenzoic acid, dinitro benzoic acid, dinitro salicylic acid, oxalic acid, fumaric acid, succinic acid, glutaric acid, maleic acid, malonic acid, adipic acid, aspirin and salicylic acid [120]. This resulted in nine cocrystals of which two cocrystals were found to be tautomer A and the other seven cocrystals existed as tautomer B [120].

2.7. Cocrystal hydrates, solvates, and their polymorphism

Hydrates of active pharmaceutical ingredients are considered as a specific class of solvates where water molecules are included in the crystal lattice of APIs [106]. Pharmaceutical hydrates are more common than other organic solvates due to the atmospheric humidity, the small size of water molecules, and the ability of water to act as hydrogen donor as well as acceptor. Solvates and hydrates provide a way of increasing the number of related solid forms for a cocrystal. The cocrystal systems reported in recent studies show polymorphic behavior (discussed in the previous section) and a strong tendency for solvates as well as hydrates, however, the literature concerning polymorphism in cocrystal solvates/hydrates is very rare when compared to single component crystals. Due to the limited literature, it is challenging to make any classifications with regard to this class of cocrystal. However, they can be classified on the same basis as hydrates/solvates of single component crystals [123]. Motherwell and Infantes studied the patterns of water clusters in hydrates. They classified these hydrates into discrete rings (I), chains (II), infinite chains (III), tapes (IV) and layer structures (V) (detailed discussion in the previous section) [50]. They observed that discrete chains (II) (61%) were mostly observed followed by infinite chains (III) (20%) and discrete rings (I) (9%).

Aitipamula et al. studied the polymorphic behavior of isoniazid: 4 hydroxybenzoic acid cocrystal monohydrate [124]. They observed that anhydrous isoniazid: hydroxybenzoic acid cocrystal and Form I of

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ionization: hydroxybenzoic acid cocrystal hydrate were converted to Form II of the isoniazid: hydroxybenzoic acid hydrate when held for an accelerated stability study at 40 °C and 75% RH [124], Jones et al. carried out polymorph screening of the caffeine: antranilic acid cocrystal (1:1). They revealed that this cocrystal exists as two different hydrates and seven solvates. The reported hydrates were confirmed as polymorphs [116]. The existence of isostructurality (similar crystal structure but not certainly the similar cell dimensions and chemical alignment) was also observed in the caffeine solvates. The caffeine: antranilic: tolune mono solvate was isostructural with the caffeine: antranilic: o-xylene mono solvate and the caffeine: antranilic: tolune hemisolvate was isostructural with the caffeine: antranilic: chlorobenzene hemisolvate and caffeine: antranilic: bromobenzene hemisolvate [116].

Jacobs and Amombo Noa studied cocrystals and cocrystal hydrates of vanillic acid [125]. Cocrystals involving caffeine and the methylated xanthines as co-formers showed different stoichiometries with cocrystals of vanillic acid: caffeine (1:2), vanillic acid: theophylline (2:1) and the cocrystal hydrate vanillic acid: theobromine (1:1): 2H2O. The vanillic acid: nicotinamide and vanillic acid: acrdine cocrystals displayed 1:1 M ratios and the same ratio in hydrates (2 vanillic acid: 2 nicotinamide: 2 H2O) [125]. Tan et al. studied cocrystal hydrates of nitrozafuran where they found that nitrozafuran: H2O was stable up to 166 °C and dehydration resulted in a new anhydrous cocrystal form [126]. This investigation demonstrated a new method of cocrystal screening. Mei et al. synthesized the celecoxib cocrystal with 4,4'-bipyridine and 1,2-di(4-pyridyl)ethylene as co-formers [117]. They observed that this cocrystal forms six isomorphic solvates with acetone, tetrahydrofuran, and 1,4-dioxane. These isomeric cocrystal solvates are isostructural and show the same cell parameters and similar crystal packing features (this is also discussed above as an example of packing polymorphism). Hydrogen-bond motifs were also found to be similar in all six solvates. These cocrystal solvates crystallized in the monoclinic C2/c space group. Their unit cells show similar stoichiometric ratio (1 celecoxib:1 co-former:1/2 solvent molecule) [117].

3. Factors affecting the morphous forms of single and multicomponent systems

3.1. Glass forming ability and stability

The glass forming ability and glass stability of small molecular weight APIs are considered to be crucial factors affecting their crystallization tendency [127]. Several efforts have been made to create a rule of thumb to forecast the glass forming ability of drugs. Commonly, the glass forming tendency of an API can be correlated with thermal indicators and the chemical structure, as summarized in Table 5. However, these thermal and chemical properties are not always reliable in predicting crystallization tendency.

Table 5

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Drug property</th>
<th>Glass forming property</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermal properties</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glass transition temp. Tg</td>
<td>+</td>
<td>[128]</td>
<td></td>
</tr>
<tr>
<td>Crystallization temp. Tc</td>
<td>+</td>
<td>[129]</td>
<td></td>
</tr>
<tr>
<td>Free energy ΔG, (negative)</td>
<td>+</td>
<td>[130]</td>
<td></td>
</tr>
<tr>
<td>Configurational entropy, Sc</td>
<td>+</td>
<td>[131]</td>
<td></td>
</tr>
<tr>
<td>(above Tp)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melting point/glass transition temp. Tm/gTg</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical properties</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Molecular weight</td>
<td>+</td>
<td>[127]</td>
<td></td>
</tr>
<tr>
<td>Benzene ring</td>
<td>-</td>
<td>[132]</td>
<td></td>
</tr>
<tr>
<td>Rotational bonds</td>
<td>+</td>
<td>[131]</td>
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</tr>
<tr>
<td>Branches</td>
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<td></td>
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</tr>
<tr>
<td>Molecular symmetry</td>
<td>-</td>
<td></td>
<td></td>
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<tr>
<td>H-bond acceptor/H-bond donor</td>
<td>+</td>
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<td></td>
</tr>
</tbody>
</table>

* a (+) API property correlates the glass forming ability positively, a (−) API property correlates the glass forming ability negatively.

Tg is the most frequently used property to predict the glass forming tendency [129]. The use of Tg alone has limited predictability. However, thermal properties and related chemical structure information, when treated by statistical tools, showed improved forecasting of glass forming capability. Molecular weight is another major indicator of the glass forming ability, and organic molecules with high molecular weight and complex structures usually show high glass forming ability [131]. However, drugs like haloperidol and griseofulvin have a higher tendency for crystallization (poor glass forming ability), despite their higher molecular weights compared to some other organic molecules with good glass forming ability, such as ketoprofen and procaine [127]. Baird et al. subjected many drugs to DSC heating/cooling cycles and categorized compounds into three classes on the basis of DSC results [127].

Class 1 Highly crystallizing APIs, which crystallized during the cooling cycle.

Class 2 Moderately crystallizing APIs, which crystallized during the 2nd heating cycle.

Class 3 Non-crystallizing APIs, which did not crystallize during cooling/ heating cycles.

From the classification above, it suggests that class 1 APIs are more likely to show a higher propensity for crystallization, while class 3 compounds are relatively good glass formers. The DSC based classification can provide early predictions from a simple experiment for assessing the tendency of API(s) to transform from an amorphous/glassy state to the crystalline state or to the glassy state from a crystalline state. In general, polymeric pharmaceutical excipients have a high molecular weight, a hard monomer and as a result a high Tg (e.g. polyvinylpyrrolidone (PVP) [133] and hydroxymethyl cellulose (HPMC)). As a result, polymeric excipients are relatively good glass formers compared to small molecular weight APIs.

3.2. Role of excipients and co-formers

Solid form screening, modification and particle engineering of pharmaceutical excipients and APIs have been performed using solvent evaporation [128–130], fusion (rapid heating) [131] and milling [128] techniques. During processing, excipients may be added to API for a variety of reasons, e.g. to stabilize proteins by reducing denaturation during manufacturing [132], to improve aerosolization performance of powder inhalers [68,133,134], to improve compactability of APIs [135,136] and to improve the solid state stability of amorphous solid dispersions [67]. Hence, the overall outcome after processing depends on the manufacturing route as well as the crystallization and vitrification propensity of the API and/or excipient(s)/co-former(s) in multicomponent systems [137].

Numerous methods to increase the quantity of dissolved API at the absorption site have been utilised, particularly for poorly soluble drugs. These include chemically modifying the API (e.g., using a prodrug approach), physically modifying the API (through particle size reduction) or employing crystal engineering/solid state modifications (e.g., amorphous, cocrystal or polymorphic forms) [134–136]. Generally, physicochemical properties of the API determine the most suitable method from those mentioned above.

While the amorphous form of an API alone may be too unstable (e.g. Class 2 or 3 above) to be considered suitable for inclusion in a conventional solid dosage formulation alone, polymeric excipients with high Tg may be used to stabilize the high energy amorphous form. Solid dispersions can be defined as dispersions of API/APIs in inert (hydrophilic) polymer carriers, and may be generated by solvent, fusion, or solvent-fusion methods [134]. Solid dispersions are classified on the basis of the solubility value of the API in the polymeric carrier. If the drug is dispersed at a molecular level then the system can be called a "molecular
which was not observed for form II cocrystals prepared by liquid-
torsion of the thermodynamically stable form I of the cocrystal. Spray dry-
II of the cocrystal and liquid (ethanol)-assisted milling led to the forma-
forms of sulfadimidine:4-aminosalicylic acid cocrystals (1:1) where
assisted milling and spray drying to generate two different polymorphic
single and multicomponent systems. Grossjohann et al. used liquid-
evaporation of the same systems gives rise to a mixture of
rating systems can lead to the formation of pure cocrystals. On the other
Alhalaweh and Velaga showed that spray drying of incongruently satu-
to effect mixing, particle size reduction and solid state modi-

cocrystal and coamorphous systems are also alternative formulation
approaches to enhancing drug dissolution performance and physical
stability of poorly water soluble drugs. The glass forming ability of the
co-former (API or non-API) plays a vital role in determining the forma-
formation of a coamorphous or cocrystal system. A coamorphous form
naproxen (a poor glass former) and indomethacin with improved disso-
lution rate and physical stability was developed by a melt cool method
[138]. The formation of the coamorphous system (rather than a cocrystal) can be attributed to the good glass forming ability of indo-
Lobmann et al. used amino acids as stabilizers to generate coamorphous systems with carbamazepine and indomethacin where
both are good glass formers [139].

3.3. Role of manufacturing method

Pharmaceutical excipients, APIs, and their mixtures/formulations can be processed by different techniques, including solvent-based and
fusion-based methods. Solvent-based methods depend mainly on the
preparation of a solution, suspension or emulsion of the API(s), pharma-
ceutical excipients and their mixtures. For example: fluid bed granula-
ion involves the removal of solvent from conventional formulation equipment [140]; spray drying differs from fluid bed granulation in the rapid
solvent removal in a controlled environment [141]; solvent controlled precipitation or co-precipitation is the process of evaporating the solvent from an aqueous solution; supercritical fluid technology in-
volves the use of some fluids which, at their supercritical state exhibit
combined characteristics of liquids (e.g. dissolving power) and gases
(e.g. diffusivity) [142], electrospinning involves the drawing of nanofi-
obers under high electrostatic potential; and cryogenic processing is in-
volved in freeze drying and spray freeze drying [143]. Fusion based
technologies are based on heating and mixing the API(s), pharmaceuti-
cal excipients and their mixtures, e.g. melt extrusion [144] and melt
granulation [145]. Milling and high shear milling are techniques used to
effect mixing, particle size reduction and solid state modifications
[146].

Different manufacturing methods can lead to different solid forms of
single and multicomponent systems. Grossjohann et al. used liquid-
assisted milling and spray drying to generate two different polymorphic
forms of sulfadimidine:4-aminosalicylic acid cocrystals (1:1) where
spray drying from ethanol led to the formation of the metastable form
II of the cocrystal and liquid (ethanol)-assisted milling led to the forma-
ion of the thermodynamically stable form I of the cocrystal. Spray dry-
ing was determined, by PXRD and DVS to lead to partial amorphisation,
which was not observed for form II cocrystals prepared by liquid-
assisted milling or solvent evaporation from ethanol or acetone [147].
Alhalaweh and Velaga showed that spray drying of incongruently satu-
rating systems can lead to the formation of pure cocrystals. On the other
hand, solvent evaporation of the same systems gives rise to a mixture of
solid phases of single and multicomponent systems. This evidently
demonstrated that, for incongruently saturating systems, kinetic factors
can be a more prominent driving factor than thermodynamic factors for
cocrystal formation [148].

It has been found that both coamorphisation and cocrystallisation can occur upon grinding/milling of physical mixtures of API and
coformer. The \( T_g \) of the solid solution and the processing conditions,
e.g. milling temperature, can govern the tendency of cocrystallisation and
co-amorphisation of physical mixtures. Jayasankar et al., demonstra-
ated that milling a mixture of the co-crystal components, carbamaze-
pine and saccharin, far below the expected \( T_g \) of their solid solution
provides an amorphous phase at room temperature. Moreover, they also showed that if the milling temperature was close to the \( T_g \) of
the mixture, co-amorphisation is not likely to occur due to high molecular
mobility near the glass transition, and that cocrystallisation will pre-
dominate [99].

4. Solid state characterization of hydrates, solvates and amorphous
forms

Cocrystals, their polymorphs, solvates and hydrates can be success-
fully characterized using similar advanced analytical techniques as those
conventionally used to characterize single component crystals
(Fig. 12). In general, comprehensive solid state characterization necessi-
tates the use of a combination of analytical techniques (Table 6). These
comprise primarily diffraction techniques such as single-crystal X-ray
diffraction (SCXRD), and powder X-ray diffraction (PXRD), spectrosco-
ic methods such as vibrational spectroscopy (FTIR and Raman) and solid
state NMR, and thermal methods such as polarized optical hot-stage mi-
croscopy (HSM), thermogravimetric analysis (TGA) and differential
scanning calorimetry (DSC) [149]. Dynamic vapor sorption (DVS) is
also an important technique in the case of hydrates and solvates.

The complete qualitative and quantitative analysis of amorphous
materials in terms of crystallization tendency, molecular mobility, sur-
face chemistry, crystallinity and intermolecular interactions necessi-
tes the use of a combination of analytical tools. Thermal
characterization tools such as DSC and isothermal microcalorimetry
(IMC) are important for the exploration of amorphous solids and ASDs
[150]. Dielectric spectroscopy is also becoming an important technique
for ASD characterization. Infrared spectroscopy, Raman spectroscopy,
and solid-state nuclear magnetic resonance spectroscopy (SSNMR)
validate the level of the molecular interactions among the different indi-
vidual components of ASDs and phase transformation in crystallization,
and may be used to quantify crystallinity [151]. Polarized light micro-
scopy (PLM), scanning electron microscopy (SEM), scanning transmis-
sion electron microscopy (STEM), HSM and atomic force microscopy
(AFM) analyze various morphological parameters and their spatial
phase distribution. PXRD is a well-established technique for quantifica-
ton of percentage crystallinity existing initially or transformed during
manufacturing [151]. X-ray photoelectron scattering (XPS) [152] and
inverse gas chromatography (IGC) [153] are very sensitive techniques
for surface analysis and anisotropy. DVS plays an important role in cal-
culating the hygroscopicity and the level of intermolecular interactions
[154], while TGA may be used to calculate the moisture level in the solid
form. The use of combinations of various analyzing techniques for inte-
grated information is an increasing trend.

4.1. X-ray diffraction techniques

PXRD may be used to study phase transformation related to
amorphous and crystalline phases, as it is very specific and quantitative
towards the crystalline phase [155]. Moreover, advanced instrumenta-
tion permits in situ studies of phase transformation as a function of con-
ditions provided (RH, temperature) to be performed. Many APIs can
transform into different polymorphic forms from an amorphous state
[156]. Thus, reference powder patterns for that API makes the identifi-
cation of different polymorphs possible [157–159]. The preferred orienta-
tion of crystals is considered to be the main source of error in PXRD
experiments, but this can be minimized using transmission mode anal-
ysis [160]. Quantification of the crystallinity in amorphous formulations

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using PXRD is a well-known technique. The intensity and area of diffraction peaks increase proportionally with an increase in crystallinity [161–164]. A more challenging aspect is to quantify nanocrystals in an amorphous material. Scherrer broadening (broadening of the diffraction peaks due to a reduction in crystallite size) may reduce the diffracted intensity for a crystalline material such that it becomes

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**Fig. 12.** Solid state characterization techniques for polymorphs, solvates, hydrates and amorphous forms.

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**Table 6**

Characterization techniques that have been used for cocrystals and their polymorphs, solvates, and hydrates.

<table>
<thead>
<tr>
<th>Pharmaceutical cocrystal polymorph, solvate, hydrate</th>
<th>FTIR</th>
<th>Raman</th>
<th>SSNMR</th>
<th>SCXRD</th>
<th>PXRD, synchrotron (S)</th>
<th>variable temperature (VT)</th>
<th>HSM</th>
<th>DSC</th>
<th>TGA</th>
<th>DVS</th>
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X-ray diffractometry, which includes PXRD and SCXRD, is a powerful technique used for the identification as well stoichiometric determination of crystal and cocrystal solvates and hydrates. SCXRD is considered as the ‘gold standard’ for structural characterization of crystals, cocrystals, hydrates, and solvates. The SCXRD technique determines the crystal unit cell dimensions and related space group. This also provides information on the complete three-dimensional arrangement, positions of atoms and packing of molecules in the unit cell [116,122,166,167]. Supramolecular synths can be elucidated from this three-dimensional arrangement. The SCXRD technique is based on the X-rays diffraction by the dense electrons in the crystal structure, which makes it comparatively unresponsive to H atom positions. In this scenario, neutron diffraction is an advanced alternative, which provides exact positions of H atom nuclear positions, making this an advanced and viable option for identification and quantification of hydrated cocrystals. PXRD is considered to be a reliable method for initial polymorph screening, although it sometimes fails to differentiate true polymorphs and associated pseudopolymorphs [50]. The present level of advanced instrumentation and computational software tools even allows powder X-ray diffraction to be used for structural characterization of crystalline solids, without the prerequisite for single crystals [168,169]. PXRD provides a fingerprint of diffraction data for a crystal form which can be further refined using Rietveld [170]. This structure solution provides a complete three-dimensional crystal arrangement, although the quality cannot be compared with the data obtained from SCXRD. However, PXRD with Rietveld refinement is becoming a more routine approach for materials where it is difficult to grow the large single crystals that are required for SCXRD analysis [171]. Synchrotron-based XRD with higher intensity and resolution provides more precise crystal structures [172,173]. Synchrotron radiation also plays an important role in energy-dispersive X-ray diffraction based experiments. Other advancements in X-ray diffractometers, like variable temperature, high-flux sources and the variability in detectors, have dramatically reduced data collection time and orientation errors [109,174,175].

4.2. Spectroscopic techniques

Vibrational spectroscopic techniques such as infrared, near-infrared, Raman [176,177] and terahertz pulsed spectroscopy [178] have been used to study and identify molecular mobility and intermolecular interactions, H bond directed molecular associations and to determine solid state forms of APIs and pharmaceutical excipients (amorphous, polymorph, solvates, hydrates or cocrystals). The properties of amorphous and crystalline materials can be explained by studying intermolecular interactions. These molecular interactions can be studied for neutral as well as ionic cases. Neutral cases include H-bonding and van der Waals interactions. For drugs showing poor solubility, these neutral interactions are often considered to be of more relevance, however it has been revealed that ionic associated interactions also add to the overall molecular level interactions [179]. These neutral interactions can be defined on the basis of the inter-molecular distance. Intermolecular hydrogen bonding manifests as a shift in vibrational stretching bands of moieties to lower frequencies and peak broadening. Novak elucidated that vibrational peak width depends on the strength of intermolecular hydrogen bonding and the distance between atomic contacts. For instance, the full-width at half maximum and the frequency of OH stretching depends on O—H…O separation [180].

Infrared (IR) spectroscopy of crystalline samples provides a fingerprint pattern of the specific crystalline materials [181]. IR spectroscopy, also called vibrational spectroscopy, shows bond vibrational modes which depend on the material’s solid-state environment [181]. Thus analysis of crystals, cocrystals and their polymorph, hydrate/solvate forms by Fourier Transform Infrared spectroscopy (FTIR) can reveal extreme changes in energy of their vibrational bands [110]. Vibrational spectroscopy is considered as one of the simplest techniques to differentiate between cocrystals or polymorphs. It becomes more important if some particular bands (mostly functional groups) are relatively sensitive to a particular solid form. Attenuated total reflectance (ATR) IR spectroscopy can be an important technique to study surface cocrystallization however ATR-IR has its own limitation in the characterization of polymorphs as it only penetrates the surface (no bulk penetration) [181,182]. Diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS) can also be a very useful technique to determine the nature and level of the interaction of solvent with the crystal or cocrystal in a hydrate or solvate, as it is a non-invasive technique and the hydrate/solvate can remain intact during analysis [183,184]. DRIFTS also gives important information related to polymorphic quantification, but particle size dependency reduces its application. FTIR can be a useful spectroscopic technique for hydrates related to crystals or cocrystals as Raman spectroscopy has its own limitations if water molecules are present. However, Raman spectroscopy becomes more important if sample availability is a constraint, as it provides the same quality of analysis even if only a few nanograms of the sample is available.

Raman spectroscopy is a very fast process analytical technology (PAT) tool which can be used to identify solid forms in drug substance and drug products [182]. Easy sample preparation is also another advantage of Raman spectroscopy, where unprocessed sample placed in a stainless steel or glass holder just needs to be interfaced with the laser beam [185]. Raman scattering is directly related to the concentration of the scattering material, which makes it a significant technique for quantitative exploration. However, Raman becomes ineffective if the material of interest is below 1% of the bulk material and here FTIR has an advantage, as FTIR can detect materials accurately even if their concentration is below 1%. Raman spectroscopy can reveal polymorphic transitions which may not be observed during DSC analysis [110].

In recent times, Raman and SSNMR spectroscopy have shown tremendous importance and potential in the characterization of cocrystals and related polymorphs, hydrates, and solvates. These spectroscopic techniques are generally considered as complementary techniques to X-ray based diffraction techniques. X-ray diffraction based methods provide more detailed structural information, whereas SSNMR provides information related to a local molecular environment, such as the number of symmetry independent molecules and their characteristic chemical shift values related to particular solid forms [186,187]. SSNMR analyzes the surrounding environments of molecules/atoms in their solid form and can be employed to study cocrystal polymorphism. SSNMR spectroscopy is also applicable to studying solvates [50]. 2-D solid-state NMR spectroscopy is also a useful technique to distinguish between conformational polymorphs if the crystal structure cannot be determined using X-ray diffraction based techniques [188]. FTIR and Raman are the basis of chemical imaging, which makes them more important for pharmaceutical formulations as they can locate and differentiate different solid forms in the formulation [189–191]. Process induced changes like polymorphic transformation, dehydration or desolvation can be easily analyzed using chemical imaging techniques [192].

4.3. Thermal techniques

Thermal techniques are also considered vital in providing significant information when used to characterize single and multicomponent amorphous and crystalline forms including crystals, cocrystals, their polymorphs, solvates, and hydrates. DSC, TGA, and HSM are considered to be the main thermal characterization techniques of importance for solid forms.

4.3.1. Differential scanning calorimetry (DSC)

Differential scanning calorimetry is a thermoanalytical method in which the difference in the amount of heat required to increase the
temperature of a sample and reference standard is measured as a function of temperature. The heat flow evolved from or transferred to the sample is derived from the measured temperature or power difference as the end response for heat flux and power compensation DSC systems, respectively. Different endothermic transitions, such as melting, glass transition, dehydration/desolvation, and thermo-degradation consume heat, whereas exothermic procedures, such as crystallization or decomposition, release heat.

Experimental conditions can significantly affect the outcome of DSC measurements, e.g., sample size and its distribution, purge gas type, flow rate, pan type, sample and pan contact area, and the heating or cooling rate. A fast heating/cooling rate increases the sensitivity but conversely decreases the resolution. Heating or cooling at a rate that is much faster than the time scale needed for the specific process of interest (e.g., recrystallization), using fast scan DSC, hyper DSC or flash DSC, can be useful to obtain calorimetric data that provides reliable information about the initial material structure or properties [167]. Quench cooling in the DSC can be beneficial, specifically for the in situ amorphization of materials which crystallize very quickly. The sample size should be very small for fast scan rates in order to ensure good thermal contact, and to avoid a thermal gradient and associated lag [194].

With respect to amorphous materials, the application of DSC to analyze isothermal/non-isothermal crystallization of such materials has been broadly described [150,195]. On heating an amorphous material, a crystallization exotherm will usually be detected at a temperature (Tc) higher than the Tg. The exotherm may also appear during the cooling of the melt. However, various authors have reported the Tc being observed earlier than Tg for physically unstable APIs [196,197].

4.3.2. Thermogravimetric analysis (TGA)

TGA is another important thermal technique which is based on examining weight loss during heating. The heating rate can be constant, isothermal or applied in oscillatory mode. TGA is considered to be an excellent technique for studying solid form decomposition. It becomes more useful if the crystal or cocrystal involves volatile components, as quantitation of the weight loss confirms the stoichiometry [116,167]. Unfortunately, TGA only provides information about the amount of the volatile constituent, without any elemental identification of the volatiles, however, the joint technique of TGA-FTIR may be used for quantification as well as identification of the volatile component of the material under test [198]. In this advanced technique, a TGA is attached to an FTIR in such a way that the released gas/volatile component directly enters an FTIR where spectral measurements can be taken along with temperature. The TGA-FTIR interfaced technique is an important advancement for the identification as well as quantitation of residual solvent and solvates of related crystal and cocrystal forms [199].

4.3.3. Microscopy

Generally speaking, polymorphs of single component solids show differences in their morphology and the same criteria applies to polymorphs of multicomponent crystals like cocrystal polymorphs and related solvates/hydrates. Hot-stage microscopy is considered to be an important initial screening technique for observing crystallization processes. Hot-stage microscopy is based on thermal imaging which involves direct optical observation of the crystal or cocrystal solid form as a function of temperature using a polarizing lens [200]. This technique is sensitive to transitions in the solid phase, such as melting, recrystallization, and dehydration and desolvation events. The transition of the dissimilar forms is differentiated by the melting and by visual analysis with polarized light. Polymorphic transitions usually show a change in birefringence, which causes changes in optical properties. Hot-stage microscopy is also an important technique to analyze solvates by viewing the gas bubbles or liquid phase evolved from a crystal. Polymorph screening can be carried out using hot stage microscope [100,201]. Hot stage microscope coupled to DSC or with another spectroscopic technique can further increase the application of this method [50].

4.4. Dynamic vapor sorption

The investigation of moisture and solid state interactions is an interesting aspect of pharmaceutical development. DVS is important for studying the relationship between sorbed vapors and different solid forms [202]. Sorption–desorption isotherms in dynamic vapor sorption may be used to quantify the equilibrium amount of vapor sorbed or desorbed as a function of the amount of vapor present, at isothermal/isobaric conditions [147]. The vapors can be from water or any volatile solvent.

DVS can be used to investigate hydrate formation and stability. Terada et al., for example, described the stability of the caffeine-citric acid cocrystal using DVS [203]. Caffeine shows instability against moisture and forms a crystalline non-stoichiometric hydrate. Citric acid, which is the co-former in this cocrystal, when treated individually, also absorbs moisture if stored at a humidity of 75% RH. Results indicated that caffeine–citric acid cocrystal forms I and II are more robust to hydrate formation when compared to individual molecules (of API and co-former) [203].

The study of moisture induced physical changes in amorphous pharmaceuticals is critical. Gravimetric measurement of sorption-desorption as a function of RH or at isothermal conditions can provide critical information relating to the amorphous form. The main properties of an amorphous formulation or API measurable by DVS are API-carrier interactions, crystallization, glass transition, solvate formation/desorvation, etc. [154].

A beneficial use of DVS, for amorphous materials, is the qualitative and quantitative analysis of crystallinity. Due to the highly hygroscopic nature of amorphous API and hydrophilic polymers (in the case of ASDs), the exposure of an amorphous sample to high levels of humidity results in the absorption of water by polar functional moieties. This moisture initiates a glass-to-rubber transformation, which considerably increases the sample mobility. With adequate moisture sorption, this higher molecular mobility overcomes the kinetic energy barrier and initiates crystallization, which then sharply decreases the propensity for water sorption [204]. The extent of equilibrium moisture sorption at a particular RH for calibrants with known amorphous content allows for quantification. However, in some instances various accompanying phenomena, such as moisture-induced phase separation, limit the quantitative application of DVS [197].

5. Future outlook and conclusions

The characterization of different solid state forms of APIs - solvates, hydrates, and amorphous forms - is pivotal in early stage solid form screening during drug product development, not just for single component systems, but also for two component systems, i.e. coamorphous or cocrystal forms. The significant number of marketed drug products that contain amorphous and hydrated crystalline APIs and excipients, and the use of various solvent-assisted manufacturing routes, means that a fundamental understanding of pharmaceutical hydrates, solvates, and amorphous forms, and the potential for formation of these different forms for a particular API or coformer combination remains crucial.

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