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Review

An overview of recent studies on the analysis of pharmaceutical polymorphs

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ABSTRACT

Pharmaceutical solids are well known to be able to exist in different solid-state forms and there are a wide variety of solid-state analytical techniques available to characterize pharmaceutical solids and solid-state transformations. In this review, the commonly used solid-state analytical techniques, the type of information collected, and advantages and disadvantages of each technique are discussed, with the focus on their application in solid-state characterization and monitoring solid-state transformations, such as amorphization, crystallization, hydrate formation/dehydration and cocrystal formation. The information gathered from recent literature is compiled in various tables to aid the reader to get a quick overall picture about what type of phenomena have recently been studied and which analytical technique(s) have been used.

Contents

1. Introduction

It is well known and recognised that pharmaceutical solids can exist in multiple crystalline solid forms. This behavior is known as polymorphism. In solvatomorphism, the formation of various crystals is the result of solvent molecules being incorporated in the crystal structure. When water is the solvent in the crystal lattice, such crystals are known as hydrates [1]. In contrast to these crystalline materials, an amorphous solid lacks three-dimensional long-range order, but may still have short-range order present over several molecular dimensions [2].

As poor aqueous solubility is a major concern in drug development, amorphous solids offer an attractive alternative because of their higher solubility which may lead to improved dissolution rate and thus possibly a higher bioavailability [3,4]. The higher solubility of amorphous solids is due to their higher energy and molecular mobility compared to their corresponding crystalline counterpart. However, the high energy and molecular mobility also make amorphous solids physically unstable. During manufacturing operations and/or storage amorphous forms are likely to revert into the stable or a metastable crystalline form if they are not adequately stabilized. Metastable polymorphs also often exhibit better solubility than the stable polymorphic form. However, the solubility advan-

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tage of a metastable form is usually less pronounced than that of an amorphous form [5,6]. More recently, cocrystals have attracted interest from the pharmaceutical community as they offer an alternative way to overcome poor aqueous solubility without sacrificing stability. A cocrystal is defined as a multiple component crystal in which all components are solid under ambient conditions when in their pure form [7].

A recent study estimated that 80–90% of organic compounds are capable of existing in polymorphic forms [8]. Polymorphs are known to give rise to significant differences in the physicochemical properties of the compound, for example, melting point, density, morphology, solubility and colour. This in turn may have an impact on the stability (physical and chemical), bioavailability and processability during manufacturing and/or in the final product [9]. In an extreme case, an undesired polymorph can even be toxic [10]. These concerns have led to increased regulatory requirements by the Food and Drug and Administration (FDA) [11]. Since then, polymorphism has become an increasingly important research topic, both in academia and the pharmaceutical industry. It is not uncommon to observe solid-state changes due to extreme conditions used in manufacturing operations, such as extensive mechanical and thermal stress and exposure to solvents. As a result, drug product performance may be significantly altered and/or fail to meet the quality specifications. Thus, proper monitoring of solid-state forms, both qualitative and quantitative, is crucial in order to ensure high-quality products [12].

The multitude and diversity of solid forms requires a thorough understanding of solid-state phenomena that may occur in pharmaceutical materials. This can only be achieved by applying associated theories to experimental results obtained with various analytical instruments. Over the decades, the capability to analyze drug polymorphs has become increasingly convenient owing to the improvement and advancement of the technologies and software available. In this review, several commonly used analytical techniques to analyze and characterize solid pharmaceutical materials are discussed. The information gathered from recent literature is compiled in tables to aid the reader to get a quick overall picture about what type of phenomena can and have been studied, and which analytical techniques have been used. In the latter sections we look at application examples of the various analytical techniques in the qualitative and quantitative solid-state analysis of active pharmaceutical ingredients (APIs).

2. Solid-state analytical techniques

The characterization of pharmaceutical solids can be performed with a wide variety of analytical techniques. General summaries of these techniques have been described in excellent textbooks [2,13]. There is no single superior method for all cases, and the method(s) of choice for any particular case depends on the key property under investigation. Usually the preferred approach is to utilise a combination of techniques to achieve a comprehensive understanding of the solid-state properties as each technique provides unique information about the solid-state form. Brittain et al. categorized solid-state characterization techniques into those associated with the molecular level (i.e., properties associated with individual molecules), the particulate level (i.e., properties pertaining to individual solid particles) and the bulk level (i.e., properties associated with an assembly of particles) [13]. A summary of commonly used analytical techniques, including their advantages and disadvantages is given in Table 1. The emphasis in this review is on molecular and particulate level techniques.

3. Applications of different techniques in pharmaceutical solid-state analysis

In pharmaceutical research, development and manufacturing, there is no lack of examples of how solid-state analytical techniques have, in some way or other, helped scientists to better understand the pharmaceutical solids of interest (APIs and excipients). Table 2 presents an overview of pharmaceutically relevant solids and systems studied by various solid-state analytical techniques over the last decade. In this table, the examples and the reference citation are presented with a short description and a list of solid-state analytical technique(s) used in the respective study. The table is sorted alphabetically, according to the API/excipient.

Table 2 reveals that most studies (~90%) use at least two or more solid-state analytical techniques (the median is four techniques per study) to characterize the sample of interest. In these studies, usually one technique was selected from the range of molecular level techniques (i.e., spectroscopic techniques) and another from the particulate level methods (i.e., X-ray diffraction, thermal method or microscopy). The most frequently used solid-state techniques were (in descending order) (1) powder X-ray diffraction (PXRD), (2) differential scanning calorimetry (DSC)/modulated temperature DSC (MTDSC), (3) mid-infrared spectroscopy (IR) and (4) microscopy. The next routinely used techniques were Raman spectroscopy, near-infrared spectroscopy (NIR), solid-state nuclear magnetic resonance (ss-NMR) and thermogravimetric analysis (TGA)/dynamic vapour sorption (DVS). The largest number of analytical tools used for solid-state characterization in a single study was eight [14–18]. There are also studies where the researchers used only one analytical instrument [19–29]. These studies came from a larger research programme where a level of understanding of the solid-state form of the compound had already been achieved from previous work, or where data treatment tools such as chemometrics or pair distribution function (PDF) were employed to extract information from the data. Amongst the single-instrument research work, spectroscopic techniques, specifically Raman and NIR were frequently used. While most studies focused on the solid-state behavior of pharmaceuticals the same analytical techniques could also be used for other purposes, e.g., quality control testing [30], drug distribution in extrudates [31] and drug–excipient compatibility testing [32,33].

In this review, the applications of solid-state analytical techniques are divided into four categories based on the type of solid-state phenomena involved in the particular studies. These categories are polymorphism and polymorphic transformations, amorphization/recrystallization, solvate systems and cocrystals. Examples and detailed information on how various solid-state analytical techniques were used with regards to each solid-state phenomenon are given in the respective tables (Tables 3–6).

3.1. Studies involving crystal polymorphism and polymorphic transformations

Polymorphic transformations between crystalline forms of an API in, e.g., crystallization, milling and heating/cooling studies have been successfully characterized by various solid-state analytical methods (Table 3). Based on this survey the analysis of crystalline forms usually involves the use of either PXRD or a spectroscopic method or a combination thereof. The preference for PXRD and spectroscopic methods can be attributed to the unique diffraction pattern/spectra of each individual polymorphic form. PXRD directly detects crystal lattice properties. Changes in the diffraction pattern can imply the presence of a new polymorph (appearance or disappearance of polymorph-specific diffraction peaks), or a smaller change in the crystal lattice, such as the introduction of a slight disorder or change in lattice parameters (small decreases in peak intensity or minor peak shifts). Spectroscopic methods

Table 1
Analytical techniques commonly used for solid-state characterization of drugs.

Analytical techniques	Information	Advantage	Disadvantage
Molecular level			
Spectroscopies			
Mid-IR [117–119] (Fourier transformed infrared (FT-IR)/diffused reflectance infrared transmission spectroscopy (DRIFTS)/attenuated total reflectance (ATR))	- Intramolecular vibrations, H-bonding Polymorphic forms: unique bands, peak shifting Amorphous form: broadening of peaks - Complementary to Raman spectroscopy - Spatial chemical information with imaging setups	- Small sample size - Relatively fast data acquisition - Availability of spectral libraries - Instruments readily available - No sample preparation required for ATR	- Sample preparation in FT-IR and DRIFTS can induce solid-state transformation - Interference from environmental humidity
Raman [117,119–124]	- Intramolecular vibrations Polymorphic forms: unique bands, peak shifting Amorphous form: broadening of peaks - Complementary to IR spectroscopy -Spatial chemical information with imaging setups	- Small sample size - No sample preparation required - Non-destructive method - Ability to penetrate through glass containers - Insensitive to water – experiments in aqueous environment possible - Relatively fast data acquisition - Fiber optic probes available - At low frequencies Raman spectroscopy can be used to analyze particulate level properties (lattice vibrations) [125]	- Local heating of sample - Sample fluorescence - Photodegradation
Near infrared (NIR) [119,126–129]	- Overtones and combinations of vibrations in the mid-IR region - Sensitive to different water states -Spatial chemical information with imaging setups	- Fast data acquisition - Non-destructive method - No sample preparation required - Ability to penetrate glass containers - Fiber optic probes available - Can also be used for particulate level (e.g., particle size) and bulk level (e.g., water content) measurements with proper calibration	- Low sensitivity and selectivity (weak intensity) - Significant baseline slope - May require chemometrics to analyze NIR spectra
Solid-state nuclear magnetic resonance (ss-NMR) [119,130–132]	- Nuclei and chemical environment within a molecule - Molecular dynamics - Interactions; drug–drug or drug–excipients	- Non destructive method - Qualitative and quantitative without calibration	- Relatively long data acquisition time - Relatively expensive
Particulate level			
Spectroscopy			
Terahertz pulsed spectroscopy (TPS) [40–42,114,124,133,134]	- Intramolecular and lattice vibrations (phonon modes) Polymorphic forms: unique peaks Amorphous form: no spectral features	- Small sample size (5–40 mg) - Rapid data acquisition (milliseconds)	- Spectrum affected by water - Baseline slope (may or may not affect the result interpretation) - Relatively expensive - Requires pellet compression (0.5–3 mm thickness) - Particle size of 100 μm is preferred to minimize scattering
X-ray			
Powder X-ray diffraction (PXRD) [13,135–137]	- Structural information from 5 to 90°2θ Polymorphic forms: unique diffraction peaks Amorphous form: no peaks, broad halo - Degree of crystallinity - Combine with PDF to yield more structural information (i.e., differences between amorphous states and/or nanocrystalline drug)	- Sample size of >50 mg - Non-destructive method - Qualitative and quantitative	- Preferred orientation - No information about the chemical structure
Single crystal X-ray diffraction (SCXRD) [13,135–137]	See PXRD -Traditionally used to solve crystal structures	- Non-destructive method	- Requires a single crystal of >0.1 mm size [38,39]
Small angle X-ray scattering (SAXS) [138,139]	- Structural information from 0.01 to 3°2θ	- Non-destructive method - Probes relatively large-scale structures (nm to μm range)	- Conventional SAXS: relatively long data acquisition time [140] - Needs advanced interpretation of data
Thermoanalytical and gravimetric analyses			
Differential scanning calorimetry (DSC) [13,58,141,142]	- Thermal events; glass transition temperature (T_g), crystallization temperature (T_c) and melting temperature (T_m), heat capacity, heat of fusion/transition/crystallization - Interactions; drug–drug or drug–excipient	- Small sample size (~3–10 mg) - Qualitative and quantitative	- Sample is destroyed during analysis - No information on the nature of the thermal events - Unable to resolve overlapping thermal events at the same temperature

Table 1 (*Continued*)

Analytical techniques	Information	Advantage	Disadvantage
Modulated temperature differential scanning calorimetry (MTDSC) [143–145]	See DSC - Separation into reversing and non-reversing heat flow (i.e., more information available)	- Improves clarity of small (i.e., T_g) and overlapping thermal events	- More experimental variables (i.e., amplitude and period setting) - Relatively long data acquisition time - Interpretation of the 'separated' thermograms not always straightforward
Thermogravimetric analysis (TGA)/dynamic vapour sorption (DVS) [146,147]	- Transitions involving either a gain or a loss of mass - Decomposition temperature - Use in conjunction with Karl Fischer titration	- Amount of solvate/hydrate in a sample - Experimental set up is straightforward - Small sample size (~3–10 mg)	- Interference with water-containing excipients - Sample is destroyed during analysis - Unsuitable for materials that degrade at low temperatures
Isothermal microcalorimetry (IMC) [148–152]	- Heat change in a reaction, e.g., enthalpy relaxation of amorphous material (direct measurement), heat of crystallization	- High sensitivity - Qualitative and quantitative analyses - Stability study directly under the storage condition - Non destructive method	- Low specificity (i.e., interpretation of data can be difficult) - Large amount (50–500 mg) of sample required
Solution calorimetry (SC) [148,149,153]	- Heat change in a reaction, e.g., heat of solution (main), heat of wetting, heat capacity of liquids, heat capacity of solids (mixture method)	- Qualitative and quantitative analyses	- Low specificity (i.e., interpretation of data can be difficult) - Large amount (15–200 mg) of sample required - Sample cannot be recovered - Long measurement time
Microscopy			
Polarized light microscopy (PLM) [13,115,154–156]	- Crystallinity (birefringence) - Morphology, colour and crystal habit	- Small sample size (microgram amount) - Easy to use - Very little sample preparation	- Quantitative information not available
With hot/cryo/freeze drying stage	- Complementary information on phase transition/physical changes in frozen state	- Temperature variability	- Careful sample preparation is required to avoid contamination with the thermal contact liquid
Scanning electron microscopy (SEM) [13,156]	- Topographical properties	- Higher resolution than light microscopy - Small sample size (microgram amount)	- Requires sample preparation and stage condition setup (vacuum setting)
Bulk level/other			
Karl Fischer titration [157,158]	- Water content (adsorbed or hydrate) - Use in conjunction with TGA/DVS	- High sensitivity - Rapid analysis	- Sample needs to dissolve in the medium - Sample size of >50 mg is preferred
Brunauer, Emmett and Teller (BET) method [159,160]	- Surface area of the samples (the BET equation is an extension of the Langmuir equation, for multilayer adsorption)	- Analysis is simple and straightforward - Non-destructive method	- Degassing step is required to remove adsorbed water or gas molecules - Small sample size (50–100 mg); sample amount may need to be adjusted depending on the surface area of sample
Density (gas pycnometer) [13]	- True density of the sample by dividing the known mass with the measured volume	- Analysis is simple and straightforward - Non-destructive method	- Degassing step (purging with helium) is required to remove adsorbed water or gas molecule - Sample size of >50 mg is preferred

do not directly measure lattice properties, but by measuring the intra- and intermolecular interactions of the molecules in solids they also provide structural information. Numerous examples exist where polymorphic transformations were thoroughly described using PXRD and/or spectroscopic methods only [34–37]. Raman spectroscopy, Fourier transform infrared (FT-IR)-attenuated total reflection (ATR) spectroscopy and NIR spectroscopy offer practical advantages over other spectroscopic methods as no sample preparation is required prior to sample analysis. Raman and IR spectroscopy are powerful and sensitive tools for qualitative and quantitative solid-state studies because all spectral bands can be assigned to specific features of the molecule under investigation. NIR spectroscopy can be used for the differentiation of polymorphs, and with a calibration model also quantification is possible. A drawback of NIR is that the bands observed in the spectra often cannot be assigned to specific bonds in molecules. Recently, in-line/on-line analysis of polymorphic transformations by the use of fiber-optic probe instruments (most often Raman or NIR spectroscopy) has gained popularity. The great potential of such instruments for process analytical purposes has now been demonstrated and we are witnessing the applications of those for the solid-state form analysis in commercial manufacturing operations.

When in-depth characterization of crystal structure or molecular structure in the crystal is needed, single crystal X-ray diffraction (SCXRD) and ss-NMR techniques provide useful information. However, they are not as popular as the above mentioned techniques, maybe due to the fact that both are quite labour-intensive: SCXRD requires a 'perfect' single crystal of >0.1 mm [38,39]; and the preparation of such is not always an easy task. ss-NMR on the other hand requires very little sample preparation and even dosage forms can be analyzed, but an obvious downside of this technique is that the measurement time is quite long. Terahertz pulsed spectroscopy (TPS) or terahertz time-domain spectroscopy (THz-TDS) is another vibrational spectroscopic technique that has been used for various pharmaceutical applications [40]. Unlike the above-mentioned spectroscopic techniques, TPS is a particulate-level technique rather than a molecular-level technique; it directly detects lattice-level phenomena (infrared active vibrational modes in the far-infrared and sub-millimeter region of the electromagnetic spectrum), and can therefore be used for the characterization of different crystalline forms [41]. TPS can be particularly useful when investigating samples with small or uncommon structural differences that may be hard to detect with other solid-state analytical techniques [42].

Table 2
An overview of solid-state analytical techniques used to study pharmaceutical solid materials.

API/sample	Year of publication	Description of the study	Solid state analytical techniques																	
			Molecular level					Particulate level										Bulk level/other		
			Spectroscopy						X-ray			Thermal and gravimetric				Microscopy				
			Vibrational spectroscopy				Other	TPS	PXRD	SCXRD	SAXS	DSC/ MTDSC	TGA (and DVS)	IMC	SC	PLM	SEM	Karl Fischer titration	BET surface area	Density (Pycnometer)
			Mid IR	NIR	Raman	ss-NMR														
[4-(4-Chloro-3-fluorophenyl)-2-[4-(methyloxy)phenyl]-1,3-thiazol-5-yl] acetic acid [161]	2009	Characterization of polymorphs	✓			✓			✓			✓								✓
Acebrophylline [162]	2007	Characterization of polymorphism including solvatomorphism							✓			✓	✓			✓				
Acrinol [88]	2010	Polymorphism and dehydration							✓	✓		✓	✓							
Acyclovir [27]	2003	Quantitative analysis of solid drugs through blister packaging			✓															
Acyclovir and lactose [32]	2009	Drug–excipient compatibility in physical mixture and commercial tablet	✓									✓								
Aminophylline [163]	2002	Solid state decomposition reactions							✓			✓		✓		✓			✓	
Ampicilline, nitrofurantoin and compound A [78]	2008	Characterization of hydrate and salt form	✓						✓			✓	✓							
Anti-HIV UC781 [164]	2008	Characterization of drug–polymer (binary/ternary mixture) solid dispersion					✓		✓			✓								
Atorvastatin calcium [30]	2010	Quality control of commercial product							✓			✓	✓			✓	✓	✓		
Baclofen [165]	2007	Solid-state characterization	✓	✓	✓				✓			✓	✓							
Benzimidazole [166]	2005	Characterization and quantification of polymorph composition in commercial products			✓															
Berberine Cl hydrates [167]	2010	Process induced transformation	✓						✓			✓	✓				✓			
Bezafibrate [168]	2009	Characterization of polymorphs	✓						✓	✓		✓	✓			✓				
Bicifadine HCl [169]	2005	Characterization of polymorphs	✓	✓					✓			✓								
Bupivacaine HCl [170]	2010	Characterization of drug–polymer complex	✓						✓			✓					✓			
Buspirone HCl [16] [15]	2006, 2007	Characterization and quantitative analysis comparing various analytical techniques	✓			✓			✓	✓		✓	✓			✓	✓			
BVT5128 [171]	2006	Physical characterization of anhydrous and hydrate forms	✓						✓			✓	✓			✓	✓	✓		
Carbamazepine [172]	2009	Solid-state transformation during dissolution			✓				✓								✓			
Carbamazepine [19]	2007	Solvation and desolvation kinetics											✓							
Carbamazepine [173]	2007	Influence of excipients on solid-state transformation during dissolution							✓								✓			
Carbamazepine [44]	2005	Characterization of polymorphs						✓				✓								
Carbamazepine [82]	2007	Polymorph detection and quantification in binary mixtures			✓				✓				✓				✓			
Carbamazepine and piroxicam [53]	2008	Dehydration during drying		✓	✓				✓				✓					✓		
Carbamazepine, enalapril maleate, fenoprofen calcium dehydrate and indomethacin [41]	2005	Quantification of polymorphism and crystallinity						✓												
Carbamazepine–nicotinamide [115]	2007	Characterization of cocrystals			✓				✓			✓				✓				

Celecoxib [174]	2003	Characterization of polymorphs	✓					✓			✓	✓		✓	✓			
Chlorpropamide [175]	2007	Polymorphic transformation induced by mechanical activation			✓				✓		✓							
Cimetidine [176]	2002	Physical stability of amorphous drug				✓		✓			✓		✓		✓			
Cimetidine–piroxicam [177]	2010	Amorphization of drug–drug binary mixture	✓					✓										
Ciprofloxacin [28]	2001	Quantitative analysis of drug in pharmaceutical solid dosage form			✓													
Clarithromycin [178]	2002	Qualitative and quantitative analyses of polymorphs				✓		✓			✓	✓						
Cyclosporin [179]	2005	Quantitative analysis of amorphous drug in binary (amorphous–crystalline) mixture	✓															
Danazol [180]	2008	Characterization of drug–polymer solid dispersion	✓					✓			✓				✓			
Diclofenac sodium [181]	2007	Characterization of hydrate forms	✓					✓			✓	✓						
Didanosine [38]	2010	Characterization of crystal structure	✓		✓			✓	✓		✓				✓			
Diflunisal [182]	2002	Characterization of drug–polymer solid dispersion	✓					✓			✓			✓				
Dipyridamole, carbamazepine, glibenclamide, and indomethacin [183]	2005	Characterization of amorphous form prepared by various methods	✓					✓			✓	✓						
Disodium hydrogen phosphates and theophylline [90]	2003	In-line monitoring of dehydration behavior of drug during fluid bed drying		✓				✓										
Efavirenz–cyclodextrin complexes [184]	2009	Characterization of drug–cyclodextrin complexes						✓			✓				✓			
Emodepside [185]	2009	Characterization of hydrate forms	✓	✓	✓			✓			✓	✓		✓				
Enalapril salts [186]	2008	Characterization of six salt forms	✓					✓			✓	✓		✓	✓	✓		
Ephedrine and pseudoephedrine [24]	2005	Quantitative analysis of binary mixture	✓															
Famotidine [187]	2009	Quantitative analysis in binary mixture			✓			✓										
Famotidine [51]	2006	Solid-state transformation during grinding	✓								✓							
Fenofibrate [188]	2009	Solid-state structure and recrystallization behavior	✓		✓			✓			✓							
Finasteride [189]	2007	Characterization of polymorphs				✓		✓	✓									
Flufenamic acid [34]	2007	Characterization of transition temperature of an enantiotropic polymorph			✓													
Flufenamic acid and magnesium oxide [190]	2010	Quantitative analysis of binary mixture						✓						✓				✓
Flurbiprofen [22]	2006	Characterization of drug–polymer solid dispersion				✓												
Furosemide [191]	2000	Characterization of drug–polymer solid dispersion						✓			✓							

Table 2 (*Continued*)

API/sample	Year of publication	Description of the study	Solid state analytical techniques																
			Molecular level				Particulate level										Bulk level/other		
			Spectroscopy					X-ray			Thermal and gravimetric				Microscopy				
			Vibrational spectroscopy			Other	TPS	PXRD	SCXRD	SAXS	DSC/ MTDSC	TGA (and DVS)	IMC	SC	PLM	SEM	Karl Fischer titration	BET surface area	Density (Pycnometer)
			Mid IR	NIR	Raman	ss-NMR													
Hydroxyprocaine HCl, tetracaine HCl and hydroxytetracaine HCl [192]	2006	Characterization of non-stoichiometric hydrate crystals	√		√	√		√			√	√			√				
Ibuprofen and naproxen [193]	2005	Characterization of drug–polymer solid dispersion	√			√		√			√				√	√			
Ibuprofen and nicotinamide [194]	2005	Characterization of drug–hydrotrope suspension	√			√		√			√				√				
Indomethacin [195]	2006	Polymorphic transformation under high pressure				√			√		√					√			
Indomethacin [76]	2007	Quantitative analysis of ternary mixtures (two polymorphic forms and an amorphous state)		√	√														
Indomethacin and carbamazepine [70]	2009	Solid-state transformation during dissolution of amorphous drugs			√			√											
Indomethacin, ketoconazole, nifedipine, flopropione, felodipine [196]	2008	Molecular mobility of amorphous form: comparison of relaxation times obtained by DRS, calorimetric, and TSDC method									√		√						
Indomethacin, piroxicam and microcrystalline cellulose [23]	2006	Differentiating amorphous and nanocrystalline material using PXRD						√											
Indomethacin–saccharin [197]	2008	Characterization of cocrystals	√	√				√	√		√				√				
Lactose [198]	2004	Quantifying amorphous content						√					√	√					
Lactose, carbamazepine, piroxicam and theophylline [199]	2007	Characterization of hydrate systems and phase transition of hydrate to anhydrous forms					√	√											
L-Hydroxypropylcellulose, α-lactose monohydrate, pregelatinized starch, silicified microcrystalline cellulose; nitrofurantoin [200]	2005	Effect of excipients on solid-state transformations of API during wet granulation						√			√							√	
Mannitol [201]	2008	Quantitative analysis of five polymorphic forms			√			√											
Mannitol–sucrose solid mixtures (with or without histidine/NaCl/$CaCl_2$) [202]	2010	Characterization of freeze-dried mannitol–sucrose samples		√															
Mepivacaine HCl [203]	2005	Characterization of polymorphs	√					√	√		√	√							
Naproxen [204–206]	2001, 2003, 2005	Characterization of drug–polymer binary or drug–amino acid–polymer ternary system	√					√			√	√							
Naproxen [207]	2004	Characterization of drug–polymer/copolymer solid dispersion	√					√			√					√			
Nifedipine [208]	2002	Solid state characterization of nifedipine solid dispersions	√					√			√								
Nitrofurantoin [209]	2007	Polymorph screening		√	√		√	√											
Nitrofurantoin, theophylline, caffeine and carbamazepine (anhydrate and hydrate forms) [210]	2005	Quantitative analysis in binary mixtures		√	√			√								√			
Ofloxacin–oxalic acid complexes [211]	2009	Characterization of co-ground binary mixture	√			√	√	√											
Olanzapine [212]	2003	Characterization of polymorphs and hydrates				√		√	√			√							
Omeprazole sodium [213]	2009	Characterization of API in salt form	√			√		√			√	√				√	√		

PEG 4000 with various lipids [214]	2010	Crystallization of PEG 4000 in polymer–lipid systems									✓	✓								
Phenazine and mesaconic acid [215]	2007	Characterization and quantitative analysis of cocrystals					✓								✓					
Piroxicam monohydrate and carbamazepine dihydrate [53]	2008	Quantification during isothermal dehydration		✓	✓			✓					✓			✓		✓		
Prednisolone [216]	2007	Characterization of drug–polymer solid dispersion				✓		✓					✓							
Progesterone [217]	2008	Characterization of drug–cyclodextrin complex	✓		✓			✓				✓	✓					✓		✓
Progesterone [218]	2007	Characterization of drug–polymer solid dispersion prepared by freeze drying	✓		✓			✓				✓	✓				✓			
Quinapril [219]	2002	Solid state stability of amorphous drug–polymer solid dispersion system						✓								✓				
Raloxifene HCl with hydrophilic carriers (PVPs, HPMC, HPC and sodium alginate) [220]	2009	Physicochemical properties of raloxifene HCl co-ground with various hydrophilic excipients	✓					✓				✓					✓			
Ranitidine HCl [75]	2009	Quantitative analysis in a ternary mixture (two polymorphic forms and an amorphous state)			✓			✓				✓								
Rifampicin [221]	2004	Characterization of polymorphic forms	✓			✓		✓				✓	✓			✓	✓			
Roxifiban [222]	2002	Characterization of polymorphs	✓		✓	✓		✓				✓		✓						
RWJ-333369 [223]	2009	Quality control study: stability and impurity testing in OROS® formulation	✓	✓				✓												
Salmeterol xinafoate [224]	2008	Characterization of polymorphs		✓	✓			✓				✓								
Salmeterol xinafoate [45]	2008	Characterization of polymorphs						✓				✓				✓				
Sibutramine HCl monohydrate [225]	2010	Thermal behavior, decomposition kinetics and compatibility in physical mixtures	✓					✓				✓	✓				✓			
Simvastatin and indomethacin [226]	2010	Quantification of process induced disorder			✓			✓				✓								
Siramesine HCl [81]	2009	Anhydrate–hydrate, salt–base transformation during dissolution			✓			✓								✓				
Sodium *N*-(3-(aminosulfonyl)-4-chloro-2-hydroxyphenyl)-*N*-(2,3-dichlorophenyl) urea trihydrate [17]	2006	Solid state characterization of API with multiple water molecules	✓	✓		✓		✓	✓			✓	✓					✓		
Spironolactone [227]	2008	Physicochemical characterization of drug content in capsule	✓									✓	✓				✓			
Stavudine [18]	2000	Characterization of polymorphs and hydrate	✓		✓			✓				✓	✓		✓	✓		✓		
Sulfamethoxazole [29]	2000	Quantitative analysis of binary solid mixtures		✓																
Sulfamethoxazole, sulfathiazole, lactose, and ampicillin [228]	2000	Quantitative analysis of binary solid mixtures		✓				✓												

Table 2 (*Continued*)

API/sample	Year of publication	Description of the study	Solid state analytical techniques																	
			Molecular level					Particulate level										Bulk level/other		
			Spectroscopy						X-ray			Thermal and gravimetric				Microscopy				
			Vibrational spectroscopy				Other	TPS	PXRD	SCXRD	SAXS	DSC/ MTDSC	TGA (and DVS)	IMC	SC	PLM	SEM	Karl Fischer titration	BET surface area	Density (Pycnometer)
			Mid IR	NIR	Raman	ss-NMR														
Sulfathiazole [229]	2005	In-line monitoring of crystallization process and solid-state characterization of crystalline product	✓						✓											
Sulfathiazole [230]	2003	Polymorph screening and processing-induced transformation (PIT) screening		✓					✓			✓	✓							
Sulfathiazole and chlorpropamide [231]	2003	Characterization of polymorphs							✓			✓					✓			
Sulfathiazole, theophylline and nitrofurantoin [25]	2005	Characterization of anhydrous/hydrate solid form using a variable temperature method							✓											
Tacrolimus [232]	2003	Characterization of drug–polymer solid dispersion	✓						✓			✓					✓			
Terazosin HCl [233]	2006	Characterization of polymorphs and hydrates		✓		✓			✓			✓								
Theophylline [234]	2007	Monitoring of solid-state transformation during fluidization		✓	✓				✓			✓						✓		
Theophylline [21]	2007	Hydration and dehydration process			✓															
Theophylline [235]	2001	Determination of the crystal structure				✓			✓											
Theophylline [91]	2004	In-line monitoring of solid-state transformations during wet granulation		✓	✓														✓	
Theophylline and caffeine [236]	2002	Characterization of hydrate formation during wet granulation		✓	✓				✓											
Theophylline and nitrofurantoin [237]	2006	Hydrate formation during dissolution			✓				✓								✓			
Theophylline anhydrate [31]	2010	Drug distribution in solid lipid extrudates			✓												✓			
Theophylline anhydrate [84]	2008	Hydrate formation during dissolution using various setups			✓				✓											
Theophylline monohydrate [238]	2006	Dehydration pathway and kinetics with or without PVP	✓						✓			✓	✓							
Theophylline monohydrate and carbamazepine dihydrate [239]	2006	Phase stability of hydrate–anhydrate systems in the presence of excipients			✓					✓						✓				
Theophylline–nicotinamide [155]	2009	Characterization of cocrystals			✓				✓			✓	✓			✓				
Topotecan HCl [240]	2006	Characterization of hydrate forms	✓			✓			✓				✓					✓		
Trimethoprim [241]	2005	Characterization of drug–polymer complexes							✓			✓								
Trimethoprim–sulfamethoxy-pyridazine [242]	2000	Characterization of polymorphs and hydrate form							✓			✓	✓					✓		
Troglitazone [243]	2008	Drug (crystalline versus amorphous) distribution in solid dispersion			✓													✓		
Venlafaxine HCl [244]	2009	Drug–excipient compatibility in physical mixture	✓						✓			✓	✓				✓			
Venlafaxine HCl [245]	2005	Characterization of polymorphs	✓						✓			✓	✓			✓				
Vinpocetine [246]	2003	Characterization of drug–polymer (binary and ternary) solid dispersion							✓			✓					✓			
Zidovudine [33]	2003	Drug–excipient compatibility studies							✓			✓	✓							

Table 3
Selected studies involving crystal polymorphism and polymorphic transformations.

API/sample	Year	Description/results of the study	Processing method(s)	Analytical technique(s)	Comments
Acetaminophen [52]	2002	Polymorphic transformation of form III to form II upon heating above 118 °C	*In situ* heating/cooling	VT-FT-IR and DSC	
Alprazolam [50]	2007	Polymorphic transformation of alprazolam form I to form III from melt-crystallization	*In situ* heating	DSC, PLM, PXRD, VT-PXRD, SCXRD	Rietveld method was used to analyze PXRD data
API not specified [247]	2001	Polymorphic transformation of drug from form B to form D The intra-agglomerate pore volume changed from a 'multilevel' and high variation to a single with less variation pore type (form B showed a larger specific surface area than samples from form D)	Milling and accelerated stability testing conditions	SEM, porosimetry and BET surface area	The use of texture properties to determine solid-state changes of API
Carbamazepine [44]	2005	Polymorphic transformation of carbamazepine form III to form I	*In situ* heating	VT-TPS and DSC	
Chlorpropamide [175]	2007	Polymorphic interconversion between form A and C of chlorpropamide during processing	Compaction, milling and cryo-milling	PXRD, Raman probe and DSC	Quantitative analysis was carried out in this work
Cilostazol [248]	2002	Crystallization of a metastable polymorph B/C during heat–cool cycle, polymorphic transformation from form B and C to form A during dissolution study	Heat–cool cycle, dissolution study	DSC, hot-stage light microscope, PXRD, FT-IR and SCXRD	HPLC was also used in the study
Famotidine [46]	2008	Polymorphic transformation of famotidine form B to intermediate B* before converting to form A during heating	Compact compression and heating in DSC	Dispersive Raman and DSC	Quantitative analysis performed using curve fitting method; Gaussian–Lorentzian function was used for the data analysis (i.e., iterative fits to yield curves with a minimum standard error; the fractional area from each curve corresponds to the amount of the solid of interest)
Famotidine [51]	2006	Polymorphic transformation of famotidine from form B to form A via grinding	Milling	DSC, FT-IR and VT-FT-IR	
Fananserine [61]	2008	Polymorphic transformation of fananserine from form III or IV to metastable form I when milled at 25 °C; milling at 0 °C resulted in amorphous fananserine	Milling	DSC and PXRD	
Flufenamic acid [34]	2007	Polymorphic transformation of flufenamic acid below or above the transition temperature between form III and form I	Slurry experiment at various temperatures	Raman probe	Univariate analysis was employed to analyze the Raman spectra
Flufenamic acid [35]	2008	Crystallization of flufenamic acid metastable form V, and interface-mediated transformation from form V to form I, II and III (stable forms)	Crystallization	PXRD, DSC, FT-IR (ATR) and ss-NMR	Elemental microanalysis was used in this study
L-Glutamic acid [36]	2006	Solvent-mediated polymorphic transformation of L-glutamic acid α to β form	Crystallization	PXRD and PLM	
Mebendazole [43]	2005	Polymorphic transformation of mebendazole from form C to form A at high temperature	*In situ* heating	PXRD, VT-PXRD, DRIFTS and DSC	
Nitrofurantoin [209]	2007	Two polymorphic forms and a monohydrate of nitrofurantoin differentiated using hyphenated NIR–Raman spectroscopy (combined with PCA) and TPS	Crystallization from acetone–water mixtures	NIR probe, Raman probe, TPS and PXRD	PCA was used to analyze NIR and Raman data; hyphenated NIR–Raman spectroscopy was used in this study

Table 3 (*Continued*)

API/sample	Year	Description/results of the study	Processing method(s)	Analytical technique(s)	Comments
Ranitidine HCl [249]	2004	In-depth characterization of ranitidine HCl polymorphic form I and form II, tautomerism of the two polymorphs	Solvent-mediated crystallization	SCXRD, SEM, hot-stage light microscope, DSC, FT-IR, ss-NMR and PXRD	
Ranitidine HCl [47]	2006	Polymorphic transformation of ranitidine HCl form 1 to form 2 via the amorphous phase	Milling	PXRD, DSC, ss-NMR and DRIFTS	
Ritonavir and compound A [250]	2005	Screening of stable polymorphs, polymorphic transformation of both ritonavir and compound A from metastable to stable form	Crystallization from suspension	PXRD, Raman probe	PCA was used to analyze Raman data
Salmeterol xinafoate [224]	2008	Polymorphic transformation of salmeterol xinafoate form I to form II	Crystallization, *in situ* heating in DSC	PXRD, DSC, FT-Raman, Raman microscope	Simultaneous *in situ* Raman-DSC analysis was carried out in this study
Salmeterol xinafoate [45]	2008	Solvent/antisolvent crystallization resulted in salmeterol xinafoate form I, polymorphic transformation or inhibition of salmeterol xinafoate form II to form I during milling with PEG6k	Crystallization from solvent/anti-solvent, milling	PXRD, DSC and hot-stage PLM	Hot-stage-PLM: isolation of salmeterol xinofoate form II seeds of form I/form II mixture by melting salmeterol xinofoate form I at 131 °C. At 131 °C, form II crystals appear birefringent against droplets of molten form I
Sulfamerazine [251]	2008	Inhibition of polymorphic transformation from form I to form II using small amount of impurities	Crystallization	Raman probe, PXRD and SEM	
Sulfathiazole [230]	2003	NIR spectroscopy was found to be useful for polymorph screening. Various polymorphic forms of sulfathiazole were observed, and the processing-induced transformations were identified	Crystallization, milling (planetary ball mill) and compression	PXRD, VT-PXRD, DSC, TGA, FT-NIR	PCA was used to analyze the NIR spectra
Sulfathiazole [252]	2009	Polymorphic transformation of sulfathiazole from form III to form I, and characterization of transition temperature	*In situ* heating in DSC	PXRD, DSC, FT-NIR, NIR probe and Raman probe	Simultaneous *in situ* Raman-DSC analysis was carried out in this study
Sulfathiazole [49]	2010	Sulfathiazole was found to crystallize as mixture of polymorphs, despite the recipe for pure polymorph crystallization was followed	Crystallization from organic solvent	DSC and hot-stage light microscope	Use of light intensity (from light microscopy) as an alternative tool for qualitative analysis
Tetrapeptide [48]	2004	Polymorphic transformation of tetrapeptide form B to form D	Accelerated stability testing conditions (i.e., temperature and humidity)	DSC, PXRD, DVS and IMC	
Theophylline [37]	2006	Polymorphic transformation of theophylline form II to form I	*In situ* heating	Terahertz time-domain spectroscopy, IR and PXRD	
Tolbutamide [253]	2006	Selective crystallization of tolbutamide form IV in cyclodextrin solution, while crystallization of form I was observed in the absence of cyclodextrin solution	Crystallization from solvent	PXRD and light microscope	

Thermal methods also provide fundamental information on polymorphic systems. The by far most popular thermal technique in characterizing polymorphs is DSC. Physicochemical properties such as the transition temperature (i.e., to determine enantiotropic/monotropic relationships between polymorphic forms) or melting temperature can be easily observed as an exothermic/endothermic event in the DSC thermograms; for instance, the polymorphic transformation of mebendazole form C to form A (around 205–220 °C) [43], melt-crystallization/transformation of carbamazepine form III to form I (130–160 °C) [44] and of salmeterol xinofoate form I to form II (121–130 °C) [45]. Quantitatively, DSC combined with Gaussian–Lorentzian curve-fitting has been used to quantify binary mixtures of famotidine polymorphs after various compression treatments [46]. Clearly, DSC is an invaluable tool when it comes to understanding the thermal properties of solid forms. However the interpretation of the thermogram may become difficult when two or more thermal events overlap or are very close to each other. The reported onset of the melting temperatures for ranitidine HCl form 1 and form 2 ranges between 134 and 140 °C and 140 and 144 °C, respectively [47]. Evidently, employing another technique such as PXRD, FT-IR or Raman spectroscopy may vastly increase the confidence in differentiating the two polymor-

Table 4
Selected studies involving amorphization and recrystallization.

API/sample	Year	Description/results of the study	Processing method(s)	Analytical technique(s)	Comments
Acetaminophen (paracetamol) [68]	2008	Crystallization of amorphous acetaminophen to form III followed by polymorphic transformation to form II	*In situ* heating	PXRD, Raman microscope, DSC	Chemometrics used in the analysis, simultaneous Raman-DSC was used in this study
Cephalothin [73]	2005	Crystallization of cephalothin from a tert-butyl alcohol–water cosolvent system during lyophilization	*In situ* freeze drying	DSC, PXRD, VT-PXRD (equipped with vacuum stage) and SEM	Quantitative analysis carried out using gas chromatography
Chlorpropamide, carbamazepine and tolbutamide [254]	2006	Study of partial disorder on tablet surfaces of three APIs	Tablet compaction and exposure to water–ethanol environment to facilitate crystallization	DSC, grazing-angle PXRD, density measurement	Polymorphic transition from form A to form C observed in chlorpropamide tablet
Dexketoprofen Trometamol [255]	2006	Amorphization of polymorph A or B during granulation process	Wet granulation	NIR, PXRD and DSC	Multivariate curve resolution–alternating least squares used to analyze the NIR spectra
Etoricoxib [66]	2007	Stabilization of amorphous etoricoxib by drug–gelucire® or drug–lipid matrix formulation	Spray drying and granulation	TGA, DSC and PXRD	
Indomethacin [74]	2006	Crystallization and transformation to α-indomethacin from amorphous and γ-indomethacin	Pressure-induced amorphization and crystallization (±solvent)	PXRD, DSC, SEM and ss-NMR	Quantitative analysis carried out in this work
Indomethacin [76]	2007	Quantification of ternary mixtures of crystalline (α and γ form) and amorphous indomethacin, using Raman and NIR spectroscopy in combination with multivariate modeling	Precipitation and filtration and quench cooling	PXRD, DSC, Raman probe and FT-NIR	Potential sources of error when using the vibrational spectroscopy methods was also investigated
Indomethacin and carbamazepine [70]	2009	Crystallization of amorphous indomethacin to α-form during dissolution, crystallization of amorphous carbamazepine to form I, followed by polymorphic conversion from form I to the dihydrate	Dissolution of compacts	Raman probe and PXRD	Semi-quantitative partial least squares discriminant analysis was used to follow the conversion
Indomethacin, nifedipine, ketoconazole, flopropione and felodipine [63]	2006	Study between predicted and experimental crystallization onset times above and below T_g	Quench-cooling	DSC, IMC, PLM	
Indomethacin–ranitidine HCl [65]	2008	Amorphization of indomethacin and ranitidine HCl binary system at various ratios	Co-milling	PXRD, DSC and DRIFTS	
Lactose, trehalose, mannitol, sorbitol and budesonide [256]	2007	Amorphization during milling of pure crystalline compound below the T_g of corresponding liquid, or co-milling of two miscible components	Milling	PXRD and DSC	Polymorphic transformation (stable to metastable) occurred during milling of pure crystalline compounds above the T_g of corresponding liquid
Microcrystalline cellulose, indomethacin and piroxicam [23]	2006	Differentiating true amorphous from nanocrystalline drugs using PDF analysis, better understanding of structural differences in amorphous samples prepared by various methods	Quench cooled and cryo-milling	PXRD	PDF, Rietveld method and total scattering method to analyze PXRD data
Moxalactam [62]	2007	The effect of annealing on the chemical stability of amorphous moxalactam–mannitol systems below the T_g	Freeze dried	Karl Fisher, PLM, PXRD, DSC and IMC	Degradation study of moxalactam using reverse phase HPLC method
Naproxen–cimetidine [64]	2009	Amorphization of naproxen and cimetidine binary system at various ratios, and improvement of dissolution of both drugs	Co-milling	PXRD, DSC and FT-Raman	Dissolution and stability studies were carried out

Table 4(*Continued*)

API/sample	Year	Description/results of the study	Processing method(s)	Analytical technique(s)	Comments
Paracetamol (acetaminophen) [69]	2008	Crystallization of quench cooled amorphous paracetamol	Thermal history prepared by various cooling rates, storage temperature and time, headspace environment and heating rate	DSC, Hot stage-PLM and PXRD	
Ranitidine HCl [59]	2008	Crystallization of amorphous ranitidine HCl to form 1 and form 2 under various storage conditions and seeding	Cryo-milling	PXRD and DSC	
Saquinavir [57]	2008	Differences in amorphous saquinavir samples, heat/cool cycle was found to further increase the disorder of amorphous saquinavir compared to the milling method	Milling and heat/cool cycle	PXRD, PLM, SEM, Karl Fisher, DSC, TGA, FT-NIR and FT-IR (ATR)	PXRD and Raman spectroscopy combined with PDF and PCA, respectively, were found to be useful to characterize different levels of disorder
Simvastatin [60]	2009	Quench-cooled amorphous simvastatin crystallizes faster than cryo-milled	Quench-cooling, cryo-milling and stability studies	PXRD, DRIFTS, PLM and DSC	Similar study was carried out in [257]
Simvastatin and indomethacin [226]	2010	Thermal, spectroscopic and diffractometric study of disordered solid materials	Ball milling (cold and cryo-mill) and quench cooling	PXRD, DSC, FT-Raman and HPLC	PXRD, Raman spectroscopy and DSC were used to detect various solid-state forms, PCA and PLS to perform quantitative analysis
Stavudine [67]	2009	Crystallization of amorphous stavudine to form III (hydrate) or form II (anhydrous), when exposed to temperature, in the absence or presence of moisture	Quench-cooling, evaporation-coating and stability testing	PXRD, VT-PXRD, DSC, TGA and SEM	

phic forms (Fig. 1). In one interesting study, the use of isothermal microcalorimetry (IMC) to study the polymorphic transformation of crystalline tetrapeptide form B to form D was reported. Vernuri et al. were able to demonstrate the rate of a transformation of tetrapeptide form B to form D under various temperature and humidity conditions by using the shape of the exothermic event obtained by IMC. DSC, PXRD and DVS were also used to support the findings in this study [48].

Visual observation using light microscopy (with or without polarizers) has also been shown to be a useful tool in screening of various solid-state forms, provided there are distinctive differences in morphology or crystal habit between the polymorphic forms. When combined with a variable-temperature stage, polymorphic transformations as a function of temperature can be visualized in real time. An example of such an application can be found in [49], where the polymorphic transformation of sulfathiazole form II to form I was observed (Fig. 2). The combination of a variable temperature stage with other analytical instruments such as PXRD [50], IR spectroscopy [51,52] and Raman and NIR [53,54] has also been shown to be an invaluable tool in polymorphic transformation studies.

3.2. Studies involving amorphization and recrystallization

The occurrence of amorphous drug and crystallization of amorphous drug during pharmaceutical processing such as grinding/milling, granulation, freeze drying and spray drying is an often-observed phenomenon (Table 4). Polarized light microscopy (PLM) offers a simple and quick way to detect amorphous material by observing (the lack of) birefringence in a sample. PXRD distinguishes an amorphous material from a crystalline phase based on the broad and diffuse maxima in the diffraction pattern of an amorphous material. Alternatively, pair distribution function (PDF) analysis of PXRD diffractograms can be used to determine the different types of disordered systems, as shown in a study by Bates et al. [23]. PDF analysis is a statistical mechanics method used to extract structure-related information (i.e., inter-atomic distances) from the whole PXRD pattern. The output of PDF analysis, denoted $G(r)$, calculated from two series of equations [55], is a measure of the probability of finding a neighbouring atom as a function of distance from an initial atom [23,56]. According to these researchers, nanocrystalline material is characterized by a matching but decaying inter-atomic distance peak (PDF probability versus distance plot) between initial crystalline and the disordered material; in a true amorphous solid, significant differences in the PDF traces in comparison to the crystalline form are observed [23]. Heinz et al. employed the PDF analysis to better characterize and understand the structural differences in amorphous saquinavir prepared by different methods (Fig. 3) [57].

While PXRD, PLM and spectroscopic methods are often used to detect the absence of crystalline species, the most popular direct method to detect amorphousness is DSC (Table 4) [58]; for example in the study of cryo-milled ranitidine HCl form 1 and 2 [59] and simvastatin [60]. Analysis of an amorphous phase using DSC should reveal a glass transition temperature (T_g) and/or a crystallization temperature (T_c), whereas only a melting temperature would be expected for a nanocrystalline material (even though amorphous and nanocrystalline materials may have similar diffraction patterns [23]). Other thermal events such as the glass transition temperature and crystallization temperature of amorphous materials may also play a role in understanding polymorphic transformations, especially when the transformation between polymorphs occurs via an amorphous phase [47,61]. Using thermal methods (DSC/MTDSC and IMC) combined with Kohlrausch–William–Watts (an empirical equation used to describe the summation of exponential relaxation/decay functions) or 'modified stretch exponential' curve-fitting methods, the kinetic properties such as the relaxation dynamics, τ^{β}, of amorphous drugs were studied. In two

Table 5
Selected studies involving solvate systems.

API/sample	Year	Description/results of the study	Processing method(s)	Analytical technique(s)	Comments
Acrinol [88]	2010	Dehydration of acrinol monohydrate to acrinol anhydrous AI form before transforming to acrinol AII (anhydrous) form	Heating	TGA, DTA, DSC, DVS and PXRD	Rietveld method was used to analyze PXRD data
Ampicillin, nitrofurantoin and compound A [78]	2008	Characterization of ampicillin trihydrate, nitrofurantoin monohydrate and compound A monohydrate	Crystallization of hydrate from aqueous solution	PXRD, TGA, DTA and DRIFTS	DTA/TGA data not presented in the publication
Baclofen [165]	2007	Interconversions between baclofen forms	Crystallization from water, wet massing experiments	PXRD, DSC, TGA, FT-IR, FT-NIR, Raman probe, light microscopy, SEM and DVS	
Caffeine, carbamazepine and sulfaguanidine [258]	2008	Influence of polymeric excipients in inhibiting anhydrous to hydrate transformation in slurry experiments	Slurry hydration with polymer of interest	Raman probe	Quantitative analysis carried out in this study, cross-linked poly(acrylic acid), HPMC and PVP were found to be good inhibitors
Carbamazepine [172]	2009	The effect of biorelevant dissolution media on solid-state transformations during dissolution	Dissolution studies using simulated GI fluids	Raman probe, PXRD and SEM	
Carbamazepine [173]	2007	The effect of excipients on solid-state transformations upon dissolution	Dissolution studies of carbamazepine compacts	SEM and PXRD	
Carbamazepine [82]	2007	Conversion of carbamazepine form III to the dihydrate form	Dissolution studies	PXRD, FT-Raman, SEM and TGA	
Carbamazepine [83]	2008	Conversion of carbamazepine forms to the dihydrate form, visualized using PCA and PLS	Solvent-mediated hydrate formation	FT-Raman	
Carbamazepine [93]	2006	Solution-mediated transformation of carbamazepine anhydrous form III to carbamazepine dihydrate in ethanol–water system	Crystallization	Raman probe, PXRD, PLM and SEM	Quantitative analysis was carried out in this work
Carbamazepine, piroxicam, theophylline and α-lactose monohydrate [199]	2007	Anhydrous and hydrated forms of crystalline pharmaceuticals characterized using TPS, monitoring of dehydration process of theophylline with *in situ* TPS	Heating	PXRD and TPS	
Citric acid [92]	2008	Solvent-mediated transformation from citric acid anhydrous to citric acid monohydrate	Solvent-mediated hydrate formation	Raman probe and FT-Raman	Quantitative analysis carried out in this study
Erythromycin [80]	2006	Dehydration of erythromycin dihydrate to anhydrous form	*In situ* heating	VT-PXRD, DSC, hot-stage light microscope and FT-IR	
Erythromycin [89]	2006	Transformation of erythromycin dihydrate to isomorphic dehydrate form was observed. Upon further heating, the isomorphic dehydrate melts and crystallizes as anhydrous erythromycin	*In situ* heating	VT-PXRD, hot-stage Raman, DSC and TGA	
Naproxen [86]	2005	Dehydration of dihydrate sodium naproxen to monohydrate sodium naproxen	Storage under low humidity and heating in oven	PXRD, TGA, SEM and PLM	
Piroxicam [259]	2007	Dehydration study of piroxicam monohydrate in compacts: comparison between TPS, Raman and NIR spectroscopy	Different sample preparation methods	TPS, Raman, NIR, VT-PXRD and TGA	PCA was used to analyze the spectra
Piroxicam and carbamazepine [53]	2008	Dehydration of piroxicam monohydrate and carbamazepine dihydrate to respective anhydrous forms	Isothermal dehydration	Karl Fisher, PXRD, VT-PXRD, TGA, NIR and Raman probe, and hot-stage NIR/Raman	Quantitative analysis carried out in this study

Table 5 (*Continued*)

API/sample	Year	Description/results of the study	Processing method(s)	Analytical technique(s)	Comments
Roxithromycin and dexamethasone [87]	2003	Conversion of roxithromycin-acetonitrile solvate to roxithromycin monohydrate, transformation of dexamethasone-dimethylsulfoxide solvate to dexamethasone sesquihydrate	Solvent-mediated hydration and storage conditions	PXRD, DSC, SEM, ss-NMR and Hot stage light microscope	
Siramesine HCl [81]	2009	Solution-mediated monohydrate formation from anhydrous form of siramesine HCl	Solvent-mediated hydration	SEM, BET surface area, PXRD, light microscope, Raman microscope	Dissolution test was also carried out in this study
Sodium dihydrogen phosphate and theophylline [90]	2003	The stepwise dehydration was observed by in-line NIR spectroscopy; the first step is the evaporation of water followed by dehydration of the crystal hydrates	Fluid bed dryer	PXRD and diffuse reflectance NIR	Second derivative transformations with 13-point Savitzky–Golay smoothing was used to process the NIR spectra
Sulfaguanidine, cromolyn sodium, ranitidine HCl [94]	2007	Hydrate formation of APIs successfully characterized using combined DVS-Raman spectroscopy method	Samples used as received	DVS and Raman probe	Simultaneous DVS and Raman spectroscopy study, PCA was used to analyze Raman spectra
Theophylline [21]	2007	Dehydration/hydrate formation between theophylline monohydrate and anhydrous form	Vapour sorption at various temperature and humidity	FT-Raman and TGA	Lorentzian or Gaussian functions were used on the Raman spectra
Theophylline [260]	2004	Dehydration of theophylline monohydrate to metastable anhydrous theophylline (form I*) before transformation to the stable form I	Fluid-bed drying	PXRD, VT-PXRD and FT-NIR	Peak integration of PXRD diffractograms was used for quantitative analysis
Theophylline [79]	2001	Dehydration of theophylline monohydrate and polymorphic conversion of form I to form II	Compression and storage in accelerated stability conditions	PXRD and Karl Fisher	Texture analyzer was used to study the crushing strength
Theophylline [84]	2008	Theophylline hydrate formation from anhydrous form during dissolution study using rotating disc and channel flow cell dissolution methods	Hydrate formation during dissolution	Raman probe, PXRD and SEM	
Theophylline [85]	2003	The effect of α-lactose monohydrate and microcrystalline cellulose on the transformation of theophylline anhydrous to monohydrate form	Wet granulation	Karl Fisher, PXRD, FT-NIR, Raman probe and SEM	
Theophylline [91]	2005	Transformation of anhydrous theophylline to monohydrate form	Slurry hydration, wet granulation	Raman/NIR probe and SEM	Quantitative analysis was carried out in this work
Theophylline and carbamazepine [239]	2006	Stability study of hydrate–anhydrate systems in the presence of hygroscopic and nonhygroscopic excipients at various storage conditions	Vapour-mediated transformation, effect of seeding and excipients	FT-Raman, PXRD and hot-stage and humidity-controlled light microscope	
Theophylline and nitrofurantoin [237]	2006	Hydrate formation during dissolution	Dissolution in a channel flow apparatus	Raman probe, PXRD and SEM	

examples, the stability and crystallization onset of moxalactam [62] and three other APIs (indomethacin, flopropione and felodipine) [63] were found to correlate with the relaxation dynamics or molecular mobility. A larger τ^{β} value indicates a lower molecular mobility or slower crystallization onset. Annealing was found to increase the τ^{β} value [62]. Employing combined analytical methods (PXRD, DSC with IR/Raman spectroscopy or TGA), amorphization of binary mixtures (API–API or API–polymer) were also described for naproxen–cimetidine [64], indomethacin–ranitidine HCl [65] and etoricoxib–polyglycolized glycerides (Gelucire®) [66] systems.

Monitoring of the recrystallization of amorphous API has also been illustrated using various solid-state analytical techniques. A single scan using PXRD or spectroscopic techniques not only can differentiate between crystalline and amorphous materials, but also, as mentioned, can be used to identify specific polymorphic form(s) recrystallized from the amorphous state [67–69]. The use

Table 6
Selected studies involving cocrystals.

API/sample	Year	Description/results of the study	Processing method(s)	Analytical technique(s)	Comments
AMG 517 with various cocrystal formers [261]	2008	AMG 517 with various cocrystal formers at 1:1 ratio was discovered and characterized	Slow cooling of saturated solution	DSC, TGA, PXRD, ss-NMR, DVS, and SCXRD	Cocrystal formers used were L(+)-lactic acid, *trans*-cinnamic acid, glutaric acid, *trans*-2-hexenoic acid, 2-hydroxycaproic acid, glycolic acid, 2,5-dihydroxybenzoic acid, L-(+)-tartaric acid, benzoic acid and sorbic acid
Caffeine with 1-, 3-, 6-hydroxy-2-naphthoic acid [112]	2007	Characterization of known imidazole–carboxylic acid synthon (i.e., caffeine–naphthoic acid) and an unusual carboxylic acid heterosynthon (i.e., caffeine–naphthoic acid–naphthoic acid–caffeine) cocrystal	Solution-mediated crystallization and slow evaporation	FT-IR, PXRD and SCXRD	
Carbamazepine–nicotinamide [100]	2009	Understanding the various thermodynamic phases of carbamazepine and carbamazepine–nicotinamide cocrystal during cocrystal formation	Cooling crystallization	PXRD, SEM and light microscope	
Carbamazepine–nicotinamide [107]	2009	Formation kinetics and stability of carbamazepine–nicotinamide cocrystals prepared from carbamazepine dihydrate, form I and form III	Milling	PXRD and DSC	PCA of PXRD was used to follow the cocrystal formation, stability study carried out at various storage conditions
Carbamazepine–nicotinamide [115]	2007	Formation of carbamazepine–nicotinamide cocrystal occurs via the amorphous phase	*In situ* heating	DSC, hot-stage PLM, PXRD, hot-stage Raman microscope	
Carbamazepine–saccharin [109]	2006	Formation of carbamazepine–saccharin is mediated by an amorphous phase	Milling, cryo-milling and various storage conditions	FT-IR (ATR), PXRD and DSC	
Carbamazepine–saccharin and carbamazepine–nicotinamide [101]	2008	Formation of two polymorphic forms of carbamazepine–saccharin and carbamazepine–nicotinamide cocrystal	Melt-crystallization	PXRD and FT-IR	
Compound 1-glutaric acid [110]	2006	Formation and stability of compound 1-glutaric acid cocrystal	Co-evaporation with seeding	DSC, PXRD, Raman probe and SCXRD	
Ethenzamide–3,5-dinitrobenzoic acid [262]	2010	Formation of two polymorphic forms (I – stable, II – unstable) of ethenzamide–3,5-dinitrobenzoic acid cocrystals and various cocrystal solvates similar to form II	Crystallization from solution and milling	SCXRD, PXRD, DSC, TGA, hot-stage PLM and ss-NMR	The authors also published similar work using various cocrystal formers; ethenzamide–saccharin [263], ethenzamide–gentisic acid [264] and ethenzamide–ethylmalonic acid [265]
Fluoxetine HCl–succinic, benzoic and flumaric acid [266]	2004	Formation of fluoxetine HCl with succinic acid or benzoic acid or flumaric acid cocrystal based on crystal engineering approach	Co-evaporation	PXRD, DSC, TGA, FT-Raman, DVS and SCXRD	
Ibuprofen, paracetamol, salicylic acid, fenbufen, flurbiprofen, ketoprofen and piracetam [116]	2008	Cocrystal formation of ibuprofen (R/S and S), salicylic acid, flurbiprofen and fenbufen with nicotinamide	*In situ* heating on hot-stage PLM and co-evaporation with or without seeding	PXRD, hot-stage PLM and SCXRD	
Indomethacin–saccharin [97]	2009	Different supercritical fluid methods to prepare indomethacin–saccharin cocrystals	Supercritical fluid methods	DSC, PXRD, FT-Raman and SEM	Particle size analysis carried out in this study
Indomethacin–saccharin or L-aspartic acid [113]	2008	The use of NIR and Raman spectroscopy for cocrystal screening	Liquid-assisted milling and cocrystallization from solution	PXRD, DSC, ss-NMR, FT-Raman and FT-NIR	PCA was used to analyze the NIR spectra

Table 6 (*Continued*)

API/sample	Year	Description/results of the study	Processing method(s)	Analytical technique(s)	Comments
Lamivudine–zidovudine [104]	2008	Formation of lamivudine–zidovudine 1:1 cocrystal followed by hydration of the cocrystal	Co-evaporation	SCXRD	Other combinations using various drugs and co-crystal formers were also studied
Norfloxacin saccharinate–saccharin dihydrate [106]	2008	Formation of norfloxacin salt with salt former (dihydrate form) cocrystal	Liquid-assisted grinding and cooling crystallization	DSC, PXRD and SCXRD	
Paracetamol, cholesterol, caffeine, ibuprofen and lactose [98]	2009	Cocrystal formation of (a) paracetamol–cholesterol, (b) caffeine–cholesterol, (c) cholesterol–lactose and (d) paracetamol–caffeine	Milling and supercritical fluid processing	SEM and PXRD	Semi-quantitative analysis was carried out in this study
Piracetam–dihydrobenzoic acid isomers [108]	2010	The effect of isomerism of cocrystal former on the physicochemical properties of cocrystals	Co-evaporation	PXRD, DSC, FT-IR (ATR) and SCXRD	
Spironolactone–saccharin [102]	2010	Formation of anhydrate and hemihydrates of spironolactone–saccharin. Characterization reviewed that both forms have the same crystal lattice	Grinding (mortar and pestle) (neat and liquid-assisted) and cooling crystallization	PXRD, SCXRD, TGA, DSC, DVS and hot-stage PLM	
Theobromine–oxalic acid [111]	2008	Real-time monitoring of theobromine–oxalic acid cocrystal formation during milling	Milling	Terahertz time-domain spectroscopy	
Theophylline, caffeine with citric acid [103]	2007	Formation of anhydrous and hydrate theophylline–citric acid cocrystal and anhydrous caffeine–citric acid cocrystals using anhydrous/monohydrate forms of theophylline, caffeine and citric acid	Milling (neat and liquid-assisted)	PXRD and SCXRD	
Tiotropium fumarate–fumaric acid salt cocrystal [105]	2009	Formation of a stable tiotropium fumarate–fumaric acid salt cocrystal at 2:1 salt ratio	Solvent/slurry crystallization	PXRD, SCXRD, DSC, FT-IR and dispersive Raman	

of on-line spectroscopic techniques (i.e., Raman and NIR) is an invaluable tool to provide rapid and non-invasive monitoring of processing-induced amorphization or crystallization. In a recent study, Savolainen et al. used in-line Raman spectroscopy (confirmed by PXRD), combined with partial least squares-discriminant analysis (PLS-DA) to monitor the crystallization processes of amorphous indomethacin (to the crystalline α-form) and amorphous carbamazepine (to form I followed by polymorphic conversion to the dihydrate form) in a dissolution study [70]. Spectroscopic monitoring of solid-state changes during a freeze-drying process has been reported [71,72], as well as *in situ* simulation of freeze-drying cycles in a variable temperature powder X-ray diffractometer (VT-PXRD) equipped with a vacuum sample stage [73].

The use of solid-state analytical methods to quantify the amount of amorphous phase in multiple-component solid mixtures has also been demonstrated; for example, PXRD [74,75], NIR [76] and Raman spectroscopy [75–77] have been used for this purpose. In most cases multivariate analysis was used. One study also looked at potential sources of error when using the vibrational spectroscopy methods [76].

3.3. Studies involving solvate systems

Studies involving transformations of solvates are summarised in Table 5. Similar to polymorphs, solvates often have unique spectra, diffraction patterns, or thermograms and thus can be easily distinguished from other solvate species or anhydrous states using the respective methods. When the distinctive morphology of a solvate/hydrate is known, visual observation (e.g., by PLM) may offer a simple and quick method for identification. Full characterization of hydrates such as ampicilin trihydrate, nitrofurantoin monohydrate and 'compound A' monohydrate has been described using PXRD, TGA, differential thermal analysis (DTA) and diffuse reflectance infrared transmission spectroscopy (DRIFTS) [78]. Dehydration experiments of piroxicam monohydrate [53], carbamazepine dihydrate [53], theophylline monohydrate [79] and erythromycin dihydrate [80] to their respective anhydrous forms, and hydration experiments (including slurry-crystallization and dissolution studies) of anhydrous siramesine HCl [81], carbamazepine form I or III [82,83] and anhydrous theophylline [84,85] to their respective mono- or di-hydrate forms have also been demonstrated. Examples of transformations between two solvates (e.g., naproxen sodium dihydrate to monohydrate) [86] and solvent exchange (e.g., roxithromycin acetonitrile to roxithromycin monohydrate and dexamethasone dimethylsulfoxide to dexamethasone sesquihydrate) [87] have also been reported.

Characterization of the dehydration transition temperature is usually carried out using two complementary methods, DSC and TGA/DVS (endothermic event in the DSC and weight loss in TGA or DVS). One advantage of the gravimetric methods (TGA and DVS) is that the weight loss (or weight gain during hydrate formation) can be used to calculate the stoichiometric water content in the API. Using DSC and TGA, it was found that arcinol monohydrate dehydrates between 70 and 120 °C and a total weight loss of 5.5% (w/w), equivalent to one molecule of water or monohydrate was found [88]. In another study on erythromycin dihydrate, TGA showed that two molecules of water were lost simultaneously in the pro-

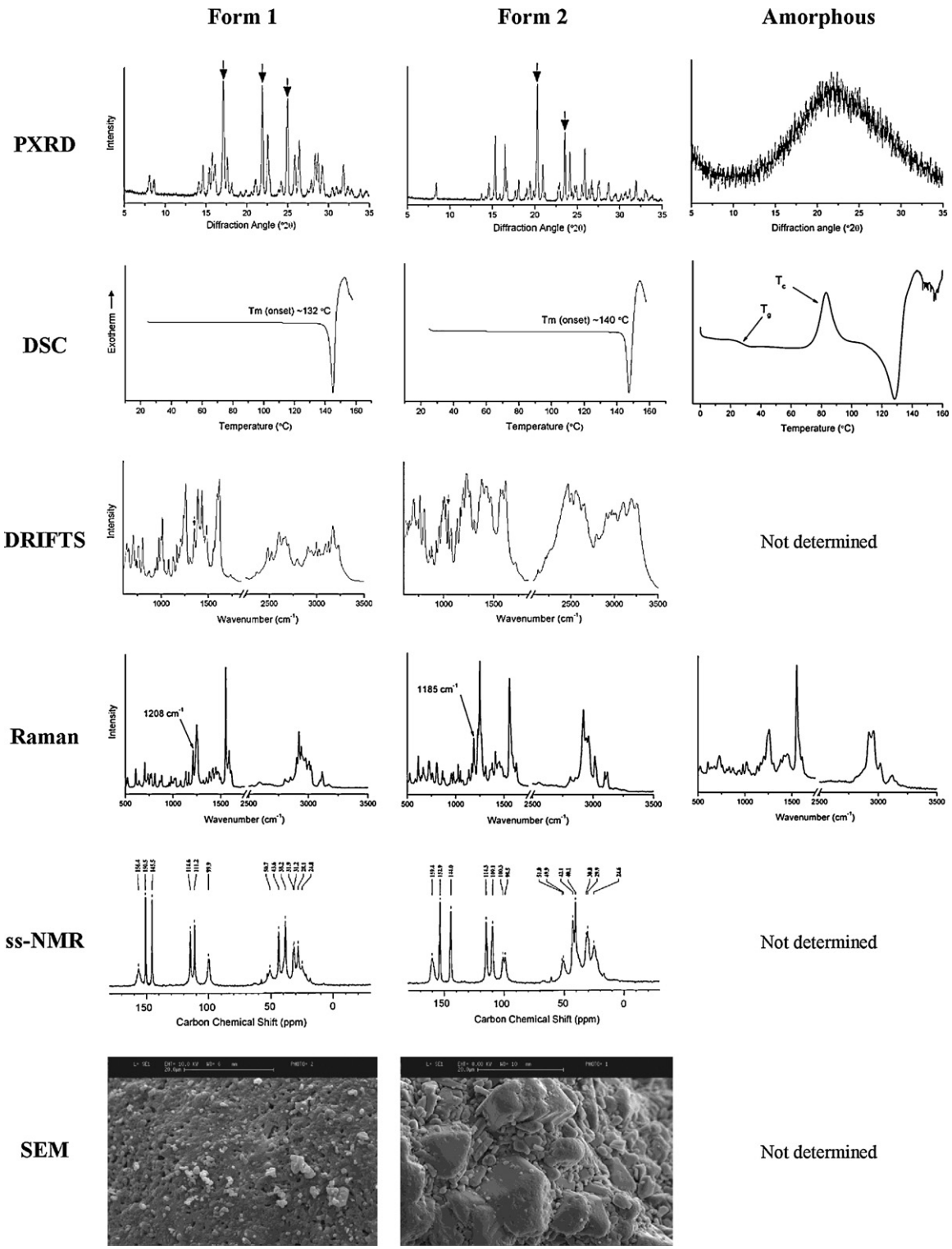

Fig. 1. Solid-state characteristics of ranitidine hydrochloride form 1, form 2 and amorphous form characterized by PXRD, DSC, DRIFTS, Raman, ss-NMR and SEM. Arrows indicate characteristic peaks of forms 1 and 2. Modified from [47].

cess between 40 and 100 °C and an isomorphic dehydrate form (e.g., very small changes in the PXRD pattern due to dehydration) was produced [89]. Non-stoichiometric hydrates or stoichiometric channel hydrates sometimes show only very small changes in their diffraction pattern due to the varying hydration state, but a TGA or DVS run clearly shows the weight loss or gain and therefore these methods provide valuable complementary information on the solid state of the sample.

The use of on-line Raman and NIR spectroscopy to monitor and quantify phase transformations during drying has also been described. In a fluid-bed drying study, Räsänen et al. used on-line NIR spectroscopy to monitor the stepwise dehydration of theophylline monohydrate by following the free water content and lattice-bound water. It was found that drying at a temperature below 40 °C resulted in the evaporation of free water, while drying above 40 °C induced dehydration of lattice-bound water

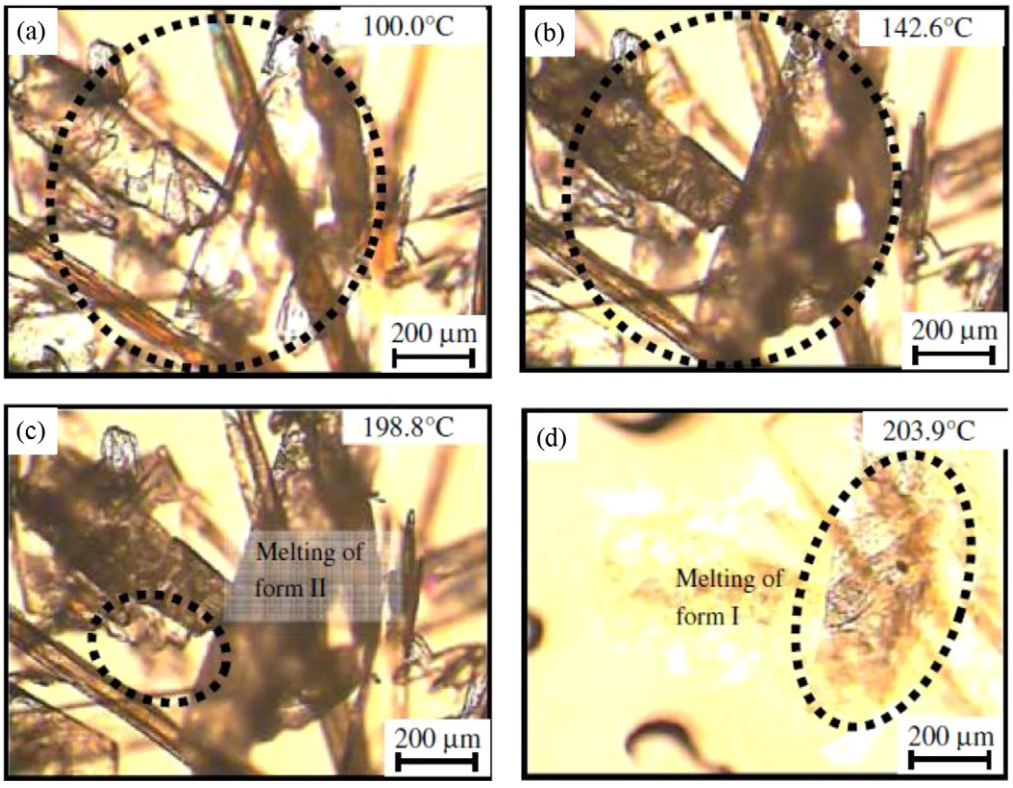

Fig. 2. Image of sulfathiazole crystals obtained during hot stage-light microscopy analysis taken at (a) 100.0 °C, (b) 142.6 °C, (c) 198.8 °C and (d) 203.9 °C. Note the optical property changes (i.e., reduce brightness and light intensity) comparing figure (a) and (b) (dotted circle region), suggesting a polymorphic transformation of form II to form I. Reprinted with permission from [49]. Copyright 2009, Springer Science+Business Media.

from theophylline monohydrate [90]. On the other hand, a wet granulation study using the same drug model found that using in-line Raman spectroscopy, but not NIR spectroscopy, it was possible to monitor the hydrate formation induced by the aqueous granulation liquid. The reason for this was that the presence of a broad water band at 1450 cm^{-1} in the NIR spectra, made it impossible to follow the transformation kinetics of anhydrous theophylline (Fig. 4) [91]. On-line Raman spectroscopy was also used in two other solution-mediated crystallization studies, citric acid and carbamazepine, where the crystallization of citric acid monohydrate and carbamazepine dihydrate was monitored and quantified. Multiplicative effects correction (MEC) and bivariate analysis were used in the quantitative analysis of citric acid suspension [92] and carbamazepine [93], respectively. Clearly, this reiterates that Raman spectroscopy is the preferred method to monitor hydrate/dehydration process in a water rich environment as it is only sensitive towards the structural changes in the API molecule, while NIR spectroscopy is perhaps more useful in characterizing hydrate crystals and free water in a dry environment. More recently, hyphenated techniques have been shown to allow fast and simultaneous solid phase analysis. Gift et al. employed DVS-Raman spectroscopy to study water–solid interactions, stoichiometric and non-stoichiometric hydrate formation of sulfaguanidine and cromolyn sodium, respectively, and the deliquescence properties of ranitidine HCl [94].

3.4. Studies involving cocrystals

Cocrystals are a long-known class of solids with unique physical properties (diffraction pattern, spectra, thermal properties and crystal habit) different from the parent solids. However, it was not until less than a decade ago, when research in this area re-emerged as pharmaceutical scientists are trying to seek for alternative solutions to improve the physical properties of APIs, e.g., stability, dissolution and bioavailability [95]. This is evident by the dramatic increase in the number of discoveries in the area of cocrystals [95]. Recent publications and reviews have presented some fascinating examples of pharmaceutical cocrystals including cocrystal polymorphs, useful guidelines for their design and synthesis as well as characterization methods used to better understand the physical properties of cocrystals [7,96]. To date, it is well accepted that the formation of cocrystals is mostly based on homosynthon (i.e., acid–acid) or heterosyn-

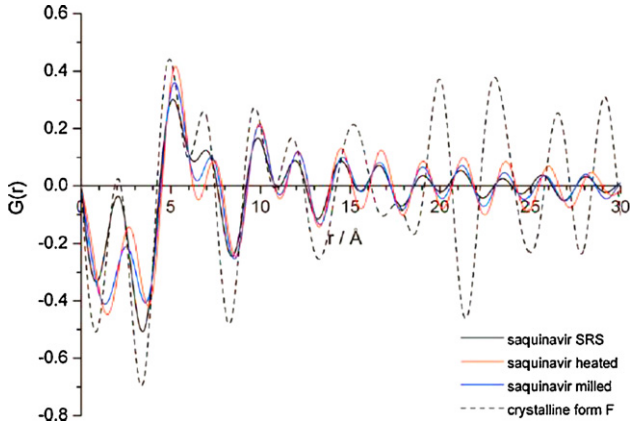

Fig. 3. Pair distribution function transforms of the PXRD data of crystalline saquinavir form F, saquinavir samples SRS from the manufacturer, milled saquinavir, and heated saquinavir showing molecular packing distances up to 30 Å. Note that the decaying height and shift of peaks of the processed samples (SRS, heated and milled) compared to the parent crystalline form (form F) are characteristics of true amorphous materials. Reprinted with permission from [57]. Copyright 2008, American Chemical Society.

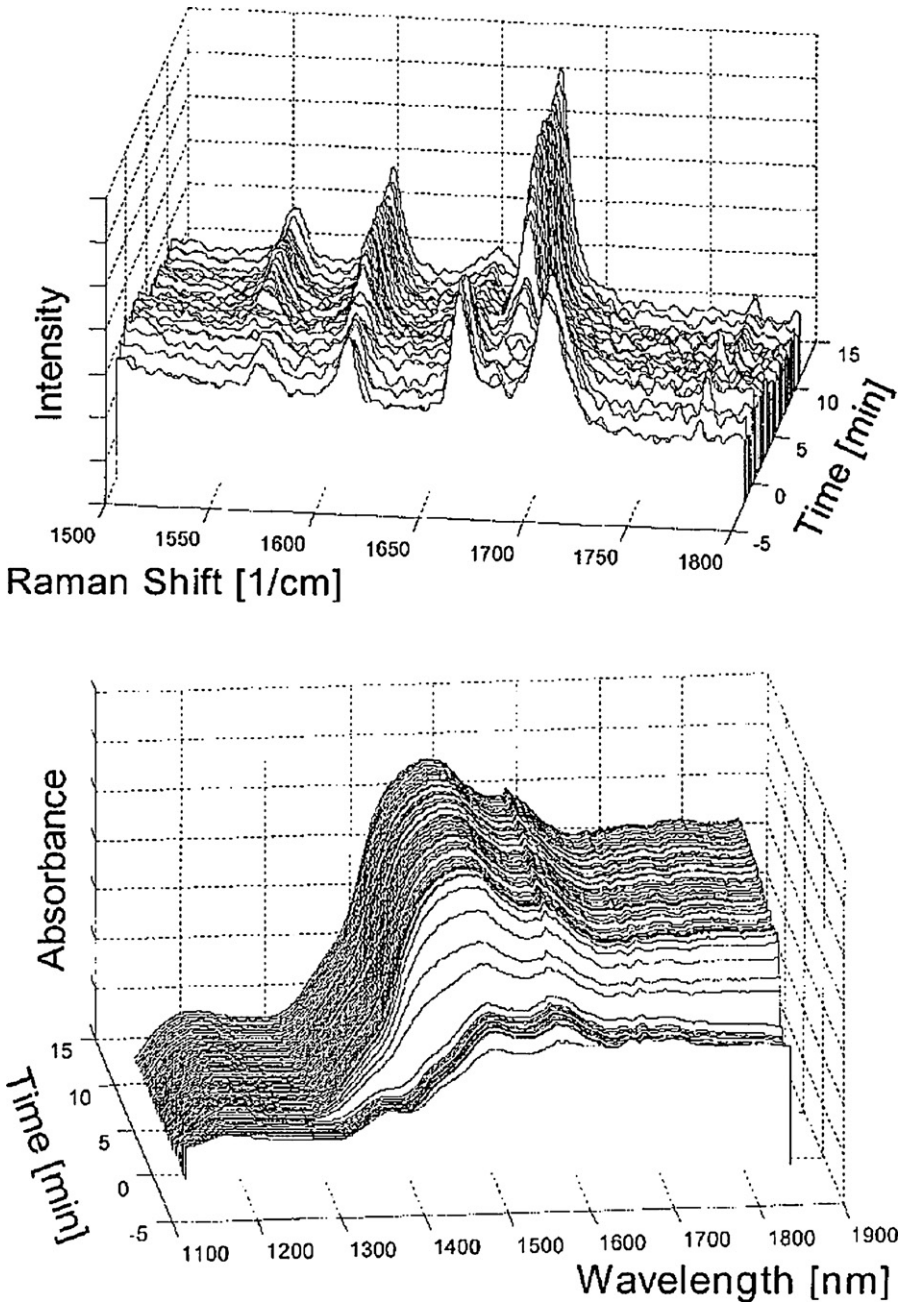

Fig. 4. Waterfall plot of Raman spectra collected during granulation showing the transformation of anhydrous theophylline with characteristic peaks at 1664 and 1707 cm^{-1} to theophylline monohydrate with a characteristic peak at 1686 cm^{-1} (top). Waterfall plot of NIR spectra collected during a granulation run highlighting the dominating effect of the water peak at 1450 nm (bottom). Reprinted with permission from [91]. Copyright 2005, John Wiley and Sons.

thon (i.e., acid–amide) formation. The commonly applied methods of cocrystallization are mechanochemical (liquid-assisted or neat grinding), solution-mediated (reaction crystallization, slurry-crystallization, co-evaporation, deliquescence in high humidity environment), and more recently supercritical fluid methods, e.g., for indomethacin–saccharin [97] and various combinations of paracetamol, cholesterol, caffeine, and lactose [98]. It has also been shown that cocrystals can form spontaneously in powder mixtures without any mechanical activation [99].

As mentioned, X-ray diffraction is by far the most popular method used to characterize crystalline materials (Table 6). PXRD allows conventional 'fingerprinting' to identify new cocrystal form(s) from a physical mixture of API and co-former. X-ray diffraction has been shown to be the key method in characterizing various cocrystal systems such as typical API–co-former cocrystals (carbamazepine–nicotinamide [100], carbamazepine/spironolactone/indomethacin with saccharin as the co-former [97,101,102]), API–co-former hydrate cocrystals (theophylline–citric acid monohydrate [103]) and API–API cocrystals (lamivudine–zidovudine [104]). Also more complicated systems have been prepared and crystallographically characterized, such as a cocrystal comprised of a salt API and a nonionized free acid moiety as the co-former (tiotropium fumarate–fumaric acid [105]), and a cocrystal consisting of a salt API, co-crystal former and two hydrate water molecules (norfloxacin saccharinate–saccharin dihydrate [106]). The use of multivariate analysis of PXRD data has also been demonstrated in the context of cocrystal formation. Using PXRD-PCA, the cocrystallization

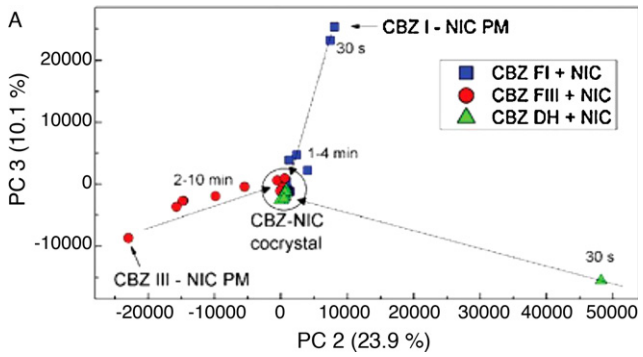

Fig. 5. PXRD-PCA score plot showing the formation pathway based on the second and third principal components. Every point on the score plot represents a PXRD pattern of carbamazepine (form 1, form 3 or dihydrate)–nicotinamide samples co-milled for various times. The arrows represent the direction of cocrystal formation, and PM denotes the physical mixture. Reprinted with permission from [107]. Copyright 2009, American Chemical Society.

pathways of carbamazepine–nicotinamide cocrystal from carbamazepine form I, III and dihydrate were followed (Fig. 5) [107].

Spectroscopic analysis can provide complementary molecular-level information to support the formation of a new cocrystal system. The spectroscopic data can present a clearly different spectrum or just slightly shifted absorption bands (relative to the parent solids) due to intermolecular interactions. Such band shifts are extremely useful in determining the specific functional groups that are involved in molecular interactions. Results of such studies have been reported for piracetam–dihydrobenzoic acid isomers (FT-IR analysis) [108], carbamazepine–saccharin (FT-IR analysis) [109], compound 1-glutamic acid (FT-Raman analysis) [110] and theobromine–oxalic acid (terahertz time domain spectroscopy analysis) [111] cocrystals. The ability of FT-IR to differentiate caffeine–hydroxy-2-naphthoic acid cocrystals from three different co-former isomers (i.e., 1 or 3 or 6-hydroxy-2-naphthoic acid) has also been demonstrated [112]. In a liquid-assisted co-milling cocrystallization study comparing off-line NIR and Raman spectroscopy combined with PCA, Allesø et al. found that Raman spectroscopy is a superior method compared to NIR spectroscopy mainly because of the low selectivity in the latter technique and the complexity of the solid samples of interest [113]. NIR spectroscopy and PCA require an additional set of reference samples before subtle differences can be differentiated [113]. Like in the case of crystalline polymorphs with very similar structures (see Section 3.1), THz-time domain spectroscopy (THz-TDS) has been used to differentiate between structurally similar cocrystals. Parrott et al. investigated isostructural cocrystals of theophylline with chiral and racemic forms of malic and tartaric acid as cocrystal formers, and concluded that THz-TDS is comparable in sensitivity to diffraction methods and more sensitive than Raman spectroscopy to changes in cocrystal architecture [114].

In addition to the X-ray diffraction and spectroscopic techniques, thermal analysis can also offer an insight into the key properties of cocrystals. While the thermograms usually exhibit a new melting point that is different from the parent solids for a fully crystallized cocrystal, DSC analysis has also been used to probe the thermal properties of intermediate stages during the cocrystallization process. Jayasankar et al. showed that cocrystal formation may be mediated through an amorphous phase as a T_g that was observed in an intermediate cryo-milled sample [109]. Seefeldt et al. also reported an intermediate amorphous phase (T_g at ~19–22 °C) of an *in situ* quench-cooled carbamazepine–nicotinamide sample, followed by a series of other thermal events (crystallization, melting and cocrystallization) before the melting endotherm of the carbamazepine–nicotinamide cocrystal at ~158 °C [115]. The multiple events were confirmed visually using hot stage PLM (Fig. 6). In another study, Berry et al. constructed a mixing zone on a hot stage PLM to screen for cocrystal formation of seven APIs with nicotinamide using a Kofler contact method (i.e., mapping of melt profile). Five APIs (ibuprofen R/S, ibuprofen S, salicylic acid, fenbufen and flurbiprofen) were visualized, and confirmed by PXRD to form cocrystal with nicotinamide [116].

4. Summary

Various analytical techniques are available to characterize and monitor the solid state of pharmaceutical materials. However, the method of choice depends on the type and depth of information required. Generally, a combination approach using at least two complementary methods is recommended. In this survey it was found that on average four techniques are used in published studies. The four most commonly used methods were PXRD, DSC/MTDSC, FT-IR spectroscopy and microscopy. Analysis using these techniques provides a good overview on the solid-state characteristics

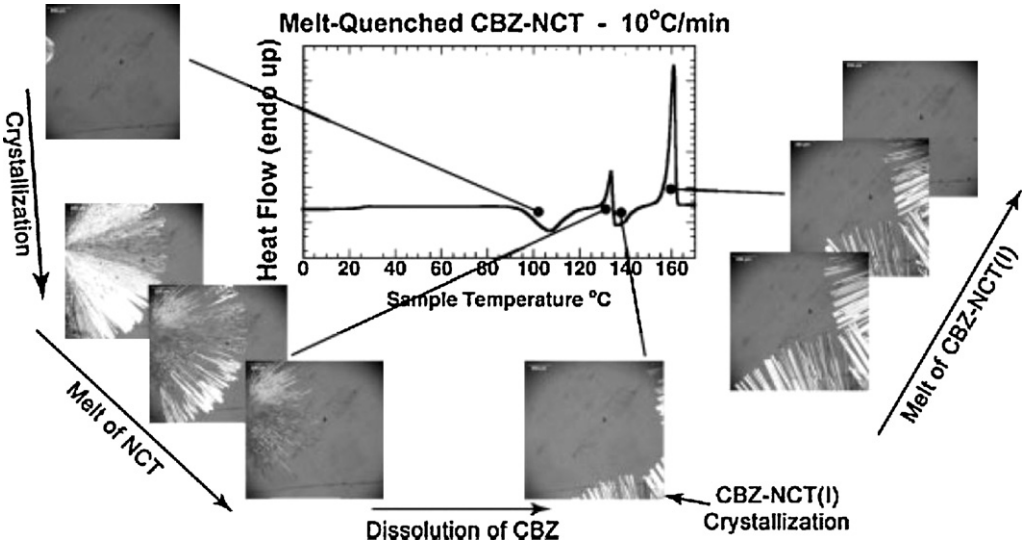

Fig. 6. DSC and hot stage-PLM results during non-isothermal crystallization studies of the amorphous phase of carbamazepine and nicotinamide at a heating rate of 10 K per min. Reprinted with permission from [115]. Copyright 2007, John Wiley and Sons.

of the sample of interest as they cover a broad range of the physicochemical properties (crystallographic, thermal, molecular and morphological, respectively). Gravimetric methods (TGA/DVS) are also commonly used to study the weight loss/gain in solvates and provide an insight into the stability of the sample. Naturally, PXRD and SCXRD are the methods of choice for crystallographic analysis. For amorphous systems, thermal methods such as DSC and IMC can differentiate amorphous from nanocrystalline and disordered crystalline systems where spectroscopic and X-ray methods may fail. Modern spectroscopic instruments equipped with fiber-optic probes are extremely useful for in-line/on-line or at-line analysis (i.e., suitable for process analytical technology (PAT) applications). Raw spectral/diffraction data can also be further processed with methods such as chemometrics or PDF analysis to further increase the sensitivity and selectivity, and thus improve the analytical capability in both qualitative and quantitative studies.

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