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Review

Analysis of solid-state transformations of pharmaceutical compounds using vibrational spectroscopy

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Abstract

Objectives Solid-state transformations may occur during any stage of pharmaceutical processing and upon storage of a solid dosage form. Early detection and quantification of these transformations during the manufacture of solid dosage forms is important since the physical form of an active pharmaceutical ingredient can significantly influence its processing behaviour, including powder flow and compressibility, and biopharmaceutical properties such as solubility, dissolution rate and bioavailability.
Key findings Vibrational spectroscopic techniques such as infrared, near-infrared, Raman and, most recently, terahertz pulsed spectroscopy have become popular for solid-state analysis since they are fast and non-destructive and allow solid-state changes to be probed at the molecular level. In particular, Raman and near-infrared spectroscopy, which require no sample preparation, are now commonly used coupled to fibreoptic probes and are able to characterise solid-state conversions in-line. Traditionally, uni- or bivariate approaches have been used to analyse spectroscopic data sets; however, recently the simultaneous detection of several solid-state forms has been increasingly performed using multivariate approaches where even overlapping spectral bands can be analysed.
Summary This review discusses the applications of different vibrational spectroscopic techniques to detect and monitor solid-state transformations possible for crystalline polymorphs, hydrates and amorphous forms of pharmaceutical compounds. In this context, the theoretical basis of solid-state transformations and vibrational spectroscopy and common experimental approaches are described, including recent methods of data analysis.
Keywords amorphous; hydrate; near-infrared spectroscopy; polymorphism; terahertz pulsed spectroscopy

Introduction

In recent decades, different physical forms of solid active pharmaceutical ingredients (APIs) have evolved from a mere scientific curiosity to an issue that must be addressed for every solid dosage form.[1–3] In crystalline materials, structural units (unit cells) are repeated in a regular manner and form a well-defined lattice. Crystalline APIs may occur in different polymorphic or solvate forms. The term polymorphism describes the ability of the crystalline substance to exist in different lattice structures and/or different molecular conformations without undergoing changes in its chemical composition. When solvent molecules are incorporated into the crystal lattice in a stoichiometric or non-stoichiometric manner, the resulting structures are designated solvates. Solvates are referred to as hydrates when water is the solvent incorporated into the crystal lattice.[1,4–6] Unlike crystalline compounds, which exhibit orientational and positional long-range order in all three dimensions of space, amorphous materials show no long-range order of molecular packing. However, local molecular assemblies characterised by short-range order may occur in the amorphous form.[5,7]

Depending on the solid-state form of an API, differences in, for example, morphology, density, stability, melting point, solubility and even colour may be observed. These differences may in turn have an impact on the API's chemical and physical stability, bioavailability and processability, involving properties such as powder flow and

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compressability. Typically, pharmaceuticals are manufactured in a stable crystalline form because the risk of solid-state transformations during storage is minimised. However, the amorphous state has attracted considerable interest in recent years because an amorphous API has a higher molecular mobility than its corresponding crystalline counterpart; this may improve the solubility and dissolution rate of poorly soluble crystalline drug candidates and thus enhance bioavailability.[2,8,9]

Whichever solid-state form is chosen, it is important for several reasons, including bioavailability, stability and patenting issues, to be able to ensure that this form is not contaminated with other solid-state forms.[10] In this context, it is important to determine the effects of processing and storage on the API, which may induce solid-state changes caused by mechanical (milling, compression) and thermal stresses or interactions with formulation components.[11] Hence, solid-state conversions must be closely monitored and trace levels of contaminating solid-state forms detected to ensure quality and efficacy of the pharmaceutical product.

The technology available to analyse pharmaceutical solid-state forms has dramatically improved recently with respect to both capability and convenience. In this review, the use of a particularly successful technology to monitor solid-state transformations – vibrational spectroscopy – is discussed. The first section describes the concept of solid-state forms and their transformations. The most commonly used vibrational spectroscopy methods are then introduced. The majority of the review considers how vibrational spectroscopy is and could be used to monitor solid-state transformations in the pharmaceutical setting.

Solid-state transformations

Solid-state conversions of pharmaceutical compounds can be classified according to their underlying mechanisms as solid–solid transformations, solution-mediated transformations, transformation via the melt of an API, and transformations from the solution of an API (Table 1).[12] Solid–solid transformations proceed directly from one solid-state form to the other, without any intermediate liquid phases. These transformations are significantly influenced by environmental conditions, including temperature, pressure and relative humidity, as well as material properties such as crystalline defects, particle size and distribution, and impurities. Solution-mediated transformations involve the dissolution of a metastable form of higher solubility. The resulting solution is supersaturated with respect to the stable crystalline polymorph, which then nucleates and grows. While the solution-mediated transformation only occurs from the metastable to the stable polymorphs of an API, transformation via solution can follow in either direction: from the metastable to the stable, or from the stable to the metastable polymorphs. In contrast to solution-mediated conversion, transformation via solution occurs when the API is dissolved and the solvent subsequently removed, which induces the phase conversion. Transformations via the melt may occur when a solid-state form of an API is melted and subsequently cooled. Depending on the nucleation rate, cooling rate, crystal growth and possible impurities, the API crystallises to the original crystalline form, to another crystalline polymorph or yields an amorphous form.[10,12]

Crystalline polymorphs

As described above, polymorphism refers to the existence of various crystalline solid forms that contain molecules of the same chemical species in the crystal lattice.[7,13] Thermodynamically, only the polymorphic form with the lowest Gibbs free energy at a given temperature and pressure is stable in those conditions and is characterised by the lowest solubility. There are two different systems of crystalline polymorphs. In enantiotropic systems the stable polymorph is different below and above a specific transition temperature (Figure 1a). The transition temperature is the temperature at which the two polymorphs have the same solubility and the free Gibbs energy is zero. In a monotropic system one of the polymorphic forms is the more stable form below the melting point of both polymorphs (Figure 1b). However, since polymorphic

Table 1 Types of solid-phase transformations

Phase transformation	Solid forms occurring	Mechanism	Processing operation
Polymorphic transformation	Crystalline form A ↔ crystalline form B	Solid–solid Solution-mediated Transformation via melt	Compression, milling, heating Crystallisation Heating above melting point and subsequent cooling
Solvation	Crystalline form → solvate	Solid–solid, solution-mediated	Crystallisation, wet granulation, pelletisation; storage in humid conditions
Desolvation	Solvate → amorphous form (harsh dehydration conditions) Solvate → crystalline form (smooth dehydration conditions)	Solid–solid	Drying operations such as fluid-bed drying, spray-drying, freeze-drying; storage in dry conditions
Amorphisation	Crystalline form → amorphous form Solvate → amorphous form (harsh dehydration conditions)	Solid–solid, solution-mediated, transformation via melt	Compression, milling, dehydration of hydrates, spray-drying, freeze-drying
Recrystallisation	Amorphous form → crystalline form	Solid–solid	Heat, humidity or plasticiser-induced crystallisation; recrystallisation upon storage

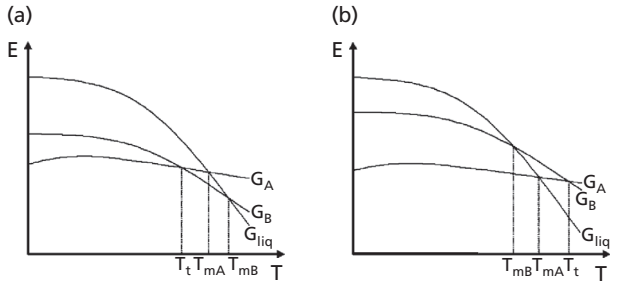

Figure 1 Energy (E)–Temperature (T) diagrams for: (a) an enantiotropic system and (b) a monotropic system. A and B subscripts refer to polymorphic forms A and B; G, Gibbs free energy; T_m, melting point; T_t, transition point between the polymorphic forms A and B. T_t for the monotropic system is virtual since it is found above T_{mA} and T_{mB}. Adapted from Brittain[7].

transformations are driven not only by thermodynamic but also by kinetic factors, even the thermodynamically metastable form may occur under specific conditions.[1,6]

Solvates

Hydrates are the most commonly observed class of solvates during pharmaceutical processing and storage of solid dosage forms, a reflection of the small size and hydrogen-bonding capability of water molecules as well as the omnipresence of water in the environment.[14] Hydrate formation processes involve the conversion of crystalline anhydrates to their hydrated forms by incorporation of water into the crystal lattice in a stoichiometric or non-stoichiometric manner and typically proceed via solution or solution-mediated mechanisms. For channel-type hydrates even solid–solid conversions are possible.[12] Solution-mediated hydrate formation processes are relevant during steps of pharmaceutical manufacturing where APIs are exposed to solvents, such as crystallisation, wet granulation, aqueous film coating, spray-drying or freeze-drying.[15] Dehydration processes typically occur via solid–solid, solution and occasionally via melt mechanisms, and the resulting material and its stability are strongly influenced by the dehydration conditions and the intrinsic properties of the hydrate.[12,16,17] During pharmaceutical processing, mechanical activation through milling or compaction may induce sufficient strain to cause deformation of the crystal lattice, and local heating also occurs, both of which may accelerate the dehydration via solid–solid mechanisms. The solution mechanism is characterised by dissolution of the API in an appropriate solvent and subsequent removal of the solvent. During the heating of an API above its melting temperature and subsequent cooling to ambient temperature, the original solid-state form is not maintained and often amorphous forms or anhydrous crystalline forms occur. In general, harsh dehydration conditions are likely to result in the formation of an amorphous form which may then crystallise to anhydrous crystal structures or a mixture of different solid-state forms. On the other hand, smooth dehydration processes, where water molecules leave the hydrate structure cooperatively, are characterised by persistence of the hydrate crystal structure during dehydration and subsequent structural reorganisation (relaxation) into the most similar crystal packing that is sufficiently stable.[18]

Amorphous materials

Amorphous phases may be generated accidentally during various steps of pharmaceutical manufacturing, such as crystallisation, milling, spray-drying, freeze-drying and compression.[2,8,15,19] When an API is melted and then cooled rapidly, the material often remains amorphous as the formation of crystallisation nuclei or sufficient crystal growth may be inhibited under these conditions. Furthermore, standard crystallisation and precipitation methods used on supersaturated solutions of APIs that show a low ability to crystallise may induce the formation of amorphous solids. During lyophilisation, amorphous materials form upon rapid freezing and crystallisation is avoided. Moreover, mechanical activation of a crystalline mass by grinding or milling leads to defects in the crystal lattice (distortions and dislocations) and structural disordering, which may result in the formation of an amorphous system.[15,19] As mentioned above, crystalline solvates may be rendered amorphous by evaporation of the solvent from the crystalline structure of a solvate and subsequent destruction of the crystal lattice.[15,19]

As the amorphous state is thermodynamically unstable, it is prone to crystallisation. Crystallisation can be regarded as a deactivation process upon which the excess energy that is stored in the amorphous system is released, accompanied by loss of entropy. Crystal nucleation and growth are influenced by several independent parameters such as temperature, humidity and solvent effects.[9,19]

Solid-state analysis using vibrational spectroscopy

Well-established analytical techniques available for characterisation of the solid state have been extensively utilised and described.[20–23] Techniques such as X-ray powder diffraction (XRPD), optical microscopy, including polarising light microscopy, scanning electron microscopy and thermal methods, including differential scanning calorimetry (DSC) and thermogravimetric analysis, have been used to characterise solid-state forms at the intermolecular level.[24]

Vibrational spectroscopic techniques such as mid-infrared (IR), near-infrared (NIR) and Raman spectroscopy have shown particular promise as tools for solid-state characterisation in the pharmaceutical setting, because they can be used to investigate differences at the molecular level and, more importantly, they are also fast, non-destructive, require no or minimal sample preparation and are suitable for remote sensing using fibreoptic technology. Terahertz pulsed spectroscopy (TPS) is a new technique, used to probe low-energy vibrations such as intramolecular torsional vibrations and intermolecular vibrations such as translations and liberations.[25] The following sections give a brief overview of the applications of these vibrational spectroscopic techniques. Applications, advantages and disadvantages of the techniques are summarised in Table 2.

Mid-infrared spectroscopy

Several commonly applied variations of IR spectroscopy are used in solid-state analysis, including attenuated total reflection (ATR) spectroscopy, which is often used to investigate aqueous samples, and diffuse reflectance Fourier transform (FT) IR spectroscopy (DRIFTS).[26] However, there is a lack of

Table 2 Vibrational spectroscopic techniques used to analyse different solid-state forms and solid-state transformations of active pharmaceutical ingredients

Vibrational spectroscopic technique	Information	Advantages	Disadvantages
FTIR spectroscopy *Modes*: Transmission DRIFTS ATR	Intramolecular vibrations *Crystalline polymorphs*: information about hydrogen bonding *Solvates*: identification of solvent *Amorphous solids*: band broadening	Structural information on molecular level No sample preparation required for ATR spectroscopy Complementary structural information to Raman spectroscopy	Sample preparation for transmission or DRIFTS experiments can induce solid-state conversions Interference of excipients and environmental humidity Probes are not yet common
NIR *Modes*: Transmission Reflectance	Overtones and combinations of intramolecular vibrations *Crystalline polymorphs and solvates*: band splitting, changes in molecular symmetry *Solvates*: loss of solvent bands during dehydration, identification of different states of water in hydrates *Amorphous solids*: band broadening, lack of low-frequency bands	No sample preparation required Rapid measurements Use of probes Possibility to measure through plastic containers	Affected by environmental water and particle size Low intensity Subtle spectral differences between different solid-state forms Broad bands and overlapping spectral regions Poor fingerprint region and hence identification more complicated than with IR or Raman spectroscopy
Raman spectroscopy *Modes*: Backscatter Transmission	Intramolecular vibrations *Crystalline polymorphs and solvates*: band shifts indicate structural changes in the crystal lattice upon polymorphic conversions and hydrate formation/de-hydration processes *Amorphous solids*: absence of spectral bands	No sample preparation required Rapid measurements Use of probes Not water sensitive, experiments in aqueous environment possible Complementary structural information to IR spectroscopy Possibility to measure through plastic containers	Local sample heating Sample fluorescence
Terahertz pulsed spectroscopy *Modes*: Transmission ATR Specular reflectance	Intramolecular vibrations, intermolecular vibrations and lattice vibrations *Crystalline polymorphs and solvates*: hydrogen bonding, low energy lattice vibrations *Amorphous solids*: bands disappear	Information about crystal structure Rapid measurements No sample preparation required for ATR measurements	Affected by water vapour Diffuse reflectance setup currently not available Spectra currently difficult to interpret because vibrational modes are not yet fully understood

ATR, attenuated total reflection; DRIFTS, diffuse reflectance Fourier transform infrared spectroscopy; FTIR, Fourier transform infrared; IR, infrared; NIR, near infrared. Adapted from Giron *et al.*[3] and Govindarajan and Suryanarayanan[11].

convenient sampling setups, in particular fibreoptic probes for remote sampling. In the last two decades, IR spectroscopy has been used to identify and characterise polymorphs and amorphous forms of various APIs [27–33] and to study interactions between APIs and excipient molecules.[34–37] Polymorphic forms[38,39] have been quantified, as well as the degree of crystallinity during pharmaceutical processing such as grinding.[40,41] Applications of IR spectroscopy for monitoring solid-state transformations are discussed in the following sections.

Near-infrared spectroscopy

NIR spectroscopy has become popular in the pharmaceutical industry in recent years for qualitative and quantitative analysis, from raw material testing to the inspection of the final manufactured product. The main reason for its popularity is the possibility for fast and non-destructive measurement of a variety of materials, including strongly absorbing and opaque solids, without any sample pretreatment.[26,42,43] Moreover, the use of fibreoptic probes allows monitoring of pharmaceutical processing on-line and in-line. In solid-state analysis, NIR spectroscopy has been applied for identification and quantification of polymorphs and amorphous forms in powder mixtures and solid dosage forms such as tablets.[44–51] It has been also used for several process analytical applications, such as moisture detection during wet granulation,[52–54] in freeze-dried solids,[55] and to describe crystallisation processes.[56] NIR spectroscopy has also become important in the study of solid-state transformations (described below).

Raman spectroscopy

Raman spectroscopy offers several advantages over IR spectroscopy, including minimal or no sample preparation. Furthermore, Raman spectroscopy analysis can be performed on solids in an aqueous environment since water is a weak Raman scatterer. In contrast to IR spectroscopy, where FT instrumentation is now almost always used, in Raman spectroscopy both dispersive and FT detection techniques are commonly used, depending on the application. Dispersive Raman spectrometers are typically operated with silicon-based charged coupled device multichannel detectors and laser

sources in the ultraviolet, visible or NIR range, while in FT Raman spectroscopy only NIR lasers are used.

Raman spectroscopy has been extensively used to characterise polymorphic and amorphous forms of pharmaceutical compounds[32,33,57–60] and to study interactions between crystalline and amorphous forms of drugs and excipients.[37] In addition to physical characterisation of APIs, in the last two decades Raman spectroscopy has become popular for the quantification of solid-state forms of APIs, including amorphous forms in powder mixtures[50,61–65] and solid dosage forms such as tablets.[66–71]

Terahertz pulsed spectroscopy

In crystalline materials terahertz radiation induces low-energy transitions within a molecule, such as torsion vibrations and intermolecular motions, including translations and liberations of molecules in the crystal lattice (phonon modes). The sensitivity of these phonon modes to differences in intermolecular forces such as hydrogen bonding networks makes TPS a valuable method for differentiation between different crystalline polymorphs.[25,72] The analysis of amorphous solids, which do not show phonon modes because of the lack of a crystal lattice and hence long-range periodicity, leads to diffuse terahertz spectra without distinct bands.[73]

TPS measurements are non-destructive and show potential for process analytical applications, since terahertz spectra of good quality can be recorded in a couple of milliseconds. Because of the low power (1 μW) of terahertz radiation, physical or chemical solid-state changes are unlikely to be induced in the samples. Furthermore, standard sampling techniques common for other vibrational spectroscopic techniques, including transmission, specular reflection, diffuse reflection and ATR, can be used in TPS.[25,74] However, at present the interpretation of terahertz spectra, including the assignment of spectral modes, is rather difficult. This is because the nuclear motions involved in the terahertz transitions are intrinsically low energy and thus are difficult to model accurately.[75–78] TPS has so far been used to identify and quantify polymorphs[73,79,80] and to characterise solid-state transformations (discussed below).[25,75,81,82]

Analysis of spectroscopic datasets

Traditionally, spectroscopic datasets have been analysed using uni- or bivariate approaches based on either heights or areas of single characteristic peaks in the spectra.[38,63,64] However, the simultaneous spectroscopic determination of several solid-state forms that occur during solid-state transformations may be particularly challenging, as specific peaks used for identification or even quantification are often overlapping or spectral differences are relatively subtle. This may be a particular problem when amorphous materials are present, since they generally show broadened and overlapping spectral bands. Moreover, non-linear relationships between spectral features and the concentration of the analytes resulting from differences in material properties, including morphology, particle size and particle density, make it more difficult to quantify different solid-state forms. To overcome these problems, multivariate methods such as principal component analysis (PCA) and partial least-squares (PLS) regression for qualitative and quantitative analysis, respectively, are used together with methods of spectral pre-processing. These chemometric approaches can extract qualitative and quantitative information from the whole spectrum. PCA is a multivariate projection method which is used to extract and display systematic variation in a data set. In PLS analysis the covariance between the spectral data and known concentration data is maximised to obtain as much information as possible, while unrelated data are neglected. This renders it possible to simultaneously analyse and quantify mixtures that contain several components with no peaks free from overlap with other peaks. More detailed information about the theory and use of multivariate analysis in pharmaceutical sciences is provided in various articles.[83–85]

Applications of vibrational spectroscopy for the study of solid-state transformations

Crystalline polymorphs

Transformations between crystalline polymorphic forms have been extensively investigated in the last two decades using vibrational spectroscopy (Table 3). In-situ Raman spectroscopy has been used to monitor solid-state transformations and to determine transition temperatures and kinetic profiles by both univariate and multivariate approaches. Several crystallisation studies have attempted to characterise solvent-mediated solid-state conversions that occur during crystallisation processes and have quantified polymorphic forms of APIs. For instance, the polymorphic conversions of the compound MK-A, which is known to exist in several anhydrous forms as well as a hemihydrate and dihydrate form, have been described using in-situ Raman spectroscopy.[86] PLS regression based on binary mixtures of two polymorphic forms was used to quantify solid-state conversions and determine conversion kinetics as well as pathways that are likely to occur during manufacturing of polymorphic form A in isopropyl acetate slurries. The effects of seeding with a polymorphic form or adding water were also investigated and in-situ Raman spectroscopy was found to be a useful tool for process development in terms of finding an optimal temperature for the preparation of the desired polymorphic form. In a similar study, the solution-mediated conversion of the metastable triclinic to the stable monoclinic crystalline form of 7-α-methyl-Δ5,10-norethindrone was investigated in acetone at room temperature using polarising light microscopy and in-situ Raman spectroscopy in the scope of a crystal growth experiment.[87] The triclinic and monoclinic forms exhibit an enantiotropic relationship and it was observed that beyond a threshold supersaturation, the triclinic form nucleated epitaxially on a small crystal of the monoclinic form and eventually converted to the stable monoclinic form.

In other crystallisation studies, the solvent-mediated conversion of L-glutamic acid was investigated using Raman microscopy,[88] in-situ Raman spectroscopy[89] and a combination of in-situ ATR-FTIR spectroscopy and Raman spectroscopy.[90] While Ferrari & Davey analysed samples taken at various stages of the crystallisation process qualitatively and only off-line[88], Ono and colleagues and Schöll and colleagues performed quantitative in-situ analysis.[89,90] Both groups performed univariate calibration based on areas of characteristic peaks using binary samples consisting of the metastable polymorph α-glutamic acid and the stable polymorph

Table 3 Applications of vibrational spectroscopy in the study of solid-state transformations of pharmaceutical polymorphs

API	Phase conversion and mechanism of conversion	Experimental	Spectroscopic technique
MK-A[86]	Polymorphic transformation of all relevant MK-A polymorphs to form A	Crystallisation experiment	In-situ Raman spectroscopy
17-Norethindrone[87]	Solvent-mediated polymorphic transformation of the triclinic to the monoclinic crystal form	Crystallisation experiment	In-situ Raman spectroscopy
L-Glutamic acid[89,90]	Solvent-mediated polymorphic transformation of α-glutamic acid to β-glutamic acid	Crystallisation experiments	In-situ Raman spectroscopy
Progesterone[88,91]	Solvent-mediated interconversion between progesterone forms I and II	Crystallisation experiment	Raman microscopy In-situ Raman spectroscopy
Flufenamic acid[92]	Solvent-mediated polymorphic transformation of flufenamic acid form III to form I	Conversion in ethanol/water solvent system	In-situ Raman spectroscopy
Carbamazepine[93]	Solid–gas–solid polymorphic transformation of carbamazepine form III to form I	Isothermal conversion monitored in an environmental chamber	In-situ Raman spectroscopy
Chloramphenicol palmitate[94]	Polymorphic transformation of crystalline form C via form B to form A	Hot stage, melting	Raman microscopy
Tamoxifen citrate[95]	Polymorphic transformation between crystalline forms I, II and III	Hot stage	Hot-stage Raman spectroscopy, Raman microscopy
Salmeterol xinafoate[96]	Polymorphic transformation between crystalline forms I and II	Heating using DSC	In-situ Raman spectroscopy
Paracetamol[97]	Polymorphic transition between crystalline forms I, II and III	Heating using DSC	Raman microscopy
Chlorpropamide[98]	Polymorphic transformation of chlorpropamide form A to form C	Conversions during compaction	In-situ Raman spectroscopy
Mannitol[100]	Polymorphic transformations between different solid-state forms of mannitol including mannitol hemihydrate, β-, and α-mannitol	Freeze-drying	Raman spectroscopy
Trovafloxacin mesylate[99,100]	Polymorphic transformation of trovafloxacin mesylate form I to form II	Conversion in hot solvent slurries	Raman and NIR spectroscopy In-situ NIR spectroscopy
SaC[102]	Polymorphic transformations between two crystalline polymorphs and an amorphous form	Crystallisation	NIR spectroscopy
Sulfathiazole[103]	Polymorphic transformation between two crystalline polymorphs	Crystallisation and mechanical treatment by milling and compaction	NIR spectroscopy
API not specified[104]	Polymorphic transformation between two crystalline polymorphs	Wet granulation	NIR spectroscopy
Fluconazole[105]	Polymorphic transformation of fluconazole form I via amorphous to form II	Heating and cooling	IR spectroscopy
Paracetamol[106]	Polymorphic transformation of paracetamol form III to form I or form II	Heating	Micro FTIR spectroscopy
Compound F[107]	Solvent-mediated polymorphic transformation of various crystalline polymorphs to crystalline form IV	Crystallisation	NIR spectroscopy
Sulfathiazole, piroxicam[108]	Polymorphic transformation between different polymorphic and amorphous form	Mechanical activation through milling	IR spectroscopy
Ranitidine hydrochloride[109]	Polymorphic transformation of ranitidine hydrochloride form I to form II via the amorphous form	Mechanical activation through milling	DRIFTS
Famotidine[110,111]	Polymorphic transformation	Mechanical activation through milling at different humidities	IR micro-spectroscopy Raman microspectroscopy
Cimetidine[112]	Polymorphic transformation of four polymorphic forms of cimetidine, dehydration of cimetidine monohydrate	Conversions induced by heating, milling, exposure to water, tableting, dry storage	IR spectroscopy
Carbamazepine[75]	Polymorphic transformation of carbamazepine form III to form I	Heating	TPS
Five forms of sulfathiazole[113]	Polymorphic transformation between different polymorphic forms	Heating	TPS
Theophylline[114]	Polymorphic transformations of polycrystalline theophylline	Heating	TPS

API, active pharmaceutical ingredient; DSC, differential scanning calorimetry; DRIFTS, diffuse reflectance Fourier transform infrared spectroscopy; FTIR, Fourier transform infrared; IR, infrared; NIR, near infrared; TPS, terahertz pulsed spectroscopy.

β-glutamic acid. The vibrational spectroscopic techniques used in all three studies confirmed the mechanism of the conversion and showed that crystals of the metastable α-form occur at first, which eventually convert to the stable β-form after dissolution of α-glutamic acid. In-situ Raman spectroscopy has also been used to investigate the solvent-mediated conversions of the monotropic system of progesterone from the metastable form II to the stable form I[91] and the enantiotropic system consisting of flufenamic acid form III and form I.[92] Wang and colleagues analysed the transformation rate of progesterone at different temperatures and found that it increases with increasing temperature.[91] Hu and colleagues aimed to determine the transition temperature and describe the transformation kinetics of flufenamic acid.[92] The solid composition at different temperatures in an ethanol/water system was examined based on a univariate calibration. By gradually narrowing the temperature range, the transition temperature could be estimated and was found to be in good agreement with the previously reported value.

In addition to various crystallisation studies, solid-state conversions were investigated using a range of experimental setups such as environmental chambers and hot stages. The isothermal conversion of carbamazepine form III to form I, for example, which is known to occur via a solid–gas–solid mechanism, was studied in an environmental chamber using in-situ Raman spectroscopy and a univariate calibration based on peak intensity ratios in binary mixtures of different amounts of the two polymorphic forms.[93] The conversion profile at different temperatures was fitted to several kinetic models, four of which gave good results that, according to the authors' conclusion, reflected the complexity of the solid-state conversion. In another study, three polymorphic forms of chloramphenicol palmitate were characterised using DRIFTS and Raman spectroscopy, and solid-state conversions between these forms were monitored upon heating, melting and cooling by hot-stage Raman microscopy.[94] Another similar study by this group showed the potential of hot-stage microscopy and Raman spectroscopy to characterise solid-state transformations between different solid-state forms of tamoxifen citrate after applying heating and cooling programmes to the drug.[95] In contrast to the previously mentioned studies, in two recent studies DSC was used to heat the samples to the desired temperatures and either in-situ Raman spectroscopy[96] or Raman microscopy[97] was used to monitor polymorphic transitions. Ali and colleagues studied the conversion between salmeterol xinafoate forms I and II and Kauffman *et al.* investigated transitions between three polymorphic forms of paracetamol.[96,97]

Another recent study investigated the mechanically induced transformation between the two structurally closely related enantiotropes of chlorpropamide as a function of the applied pressure during compaction using in-situ Raman spectroscopy.[98] A PLS regression model involving binary mixtures of the two solid-state forms was used for quantification. Overall, the spectroscopic analysis allowed the influence of compaction pressure on the polymorphic behaviour of chlorpropamide to be monitored. The study also revealed that shear stress at interparticulate interfaces was a key factor for the conversion.

Two other studies have used vibrational spectroscopy to analyse the freeze-drying process of mannitol from aqueous solution.[99,100] Both groups used in-line Raman spectroscopy and PCA, while De Beer and colleagues also used at-line NIR spectroscopy.[99] The studies aimed to monitor solid-state changes of mannitol during lyophilisation, to detect physical changes in the state of water (e.g. ice nucleation) and to determine endpoints of the different steps of lyophilisation, including freezing, primary drying and secondary drying. Romero-Torres and colleagues compared two different in-line Raman probes: one with a small laser spot size of about 150 μm diameter and the other with a much large laser spot size of about 6 mm diameter.[100] The authors confirmed the presence of various solid-state forms of mannitol, including mannitol hemihydrate, and found that the large-spot Raman probe led to more representative sampling and an improved signal-to-noise ratio. De Beer *et al.* were able to monitor the ice nucleation and mannitol crystallisation during freezing and primary drying with the help of in-line Raman spectroscopy and PCA.[99] In addition, a two-level full factorial design was used to investigate process parameters such as freezing rate, concentration of mannitol and concentration of sodium chloride on the outcome of crystallisation. Overall, NIR spectroscopy proved to be very suitable for monitoring the endpoint of ice nucleation since NIR spectroscopy is sensitive to the presence and state of water. However, because strong water absorption obscured other bands, NIR spectroscopy could not be used to describe processes that occurred before the end of the primary drying step, which means that the freezing step cannot be monitored and therefore controlled with this spectroscopic technique alone. Raman spectroscopy could resolve all of the physical phenomena and structural changes during the different freeze-drying steps, since water and ice are weak Raman scatterers.

NIR spectroscopy

NIR spectroscopy has been used to investigate solid-state conversions during different steps of pharmaceutical manufacturing, including crystallisation, milling, wet granulation and compression of crystalline samples. The conversion of trovafloxacin mesylate crystalline form I to form II in hot solvent slurries, for instance, has been analysed using in-situ NIR spectroscopy combined with PCA.[101] With the help of the PCA scores plot, the conversion could easily be followed and the authors hence concluded that on-line NIR spectroscopy and PCA are excellent tools for routine pharmaceutical process monitoring. Another crystallisation study investigated the solid-state conversions of SaC (an API produced by Sanofi-Synthèlabo), which may occur in two crystalline polymorphic forms and an amorphous form, using on-line NIR spectroscopy and principal component regression.[102] The polymorphic transitions were monitored and the effects of temperature, crystal habit, the size of the seed crystals, and small amounts of water on the rate of transformation were studied.

A study focusing on pharmaceutical processing characterised the solid state of sulfathiazole after crystallisation from different solvents and upon milling and compression of crystalline sulfathiazole samples.[103] The characterisation techniques that were used included NIR spectroscopy combined with cluster analysis and PCA, as well as XRPD and

thermal methods. The decrease of the crystalline sample content and the increase of the amorphous content upon milling and the polymorphic transition between two crystalline polymorphs of sulfathiazole upon milling were monitored. Overall, the authors concluded that vibrational spectroscopy combined with data analysis methods such as PCA represents a fast tool for polymorph screening during pharmaceutical processing.

A recent study successfully used NIR spectroscopy and a univariate quantification method to investigate the conversion between the desired and the undesired crystalline polymorphs of an API during wet granulation.[104] A quantification model was built based on samples of granulation blends consisting of the desired polymorphic form and excipients spiked with the undesired polymorphic form. The authors concluded that NIR spectroscopy is a powerful tool for fast and non-invasive analysis of solid-state transformations in powder samples during pharmaceutical processing.

Like the other spectroscopic techniques, IR spectroscopy has been used for solid-state characterisation and to monitor solid-state conversions during industrial processing steps such as crystallisation, mechanical activation and thermal treatment, including melting, cooling and reheating of crystalline APIs. In addition to other solid-state characterisation techniques such as DSC and XRPD, temperature-controlled IR spectroscopy has been used, for example, to describe the solid-state transformations of fluconazole form I during heating and subsequent cooling[105] and the temperature-induced solid-state changes of paracetamol.[106] In-situ ATR-IR spectroscopy making use of ATR immersion probes has been used to monitor cooling-induced crystallisation processes of compound 'F' and its associated solvent-mediated solid-state conversions.[107] The ATR analysis allowed determination of the concentration profiles of the polymorphic forms occurring upon crystallisation in real time. The author concluded that this approach could be valuable for in-process control of crystallisation processes during pharmaceutical manufacturing and might reduce batch-to-batch variability through early detection of unwanted impurities.

Further studies have investigated the behaviour of sulfathiazole, piroxicam,[108] ranitidine hydrochloride[109] and famotidine[110] during mechanical activation using IR spectroscopy. When the crystalline sulfathiazole was milled, it initially lost some crystallinity but then recrystallised, with conversions between crystalline forms occurring.[108] Similar to sulfathiazole, crystalline β-piroxicam underwent partial amorphisation, which was accompanied by a change from white to yellow. Chieng *et al*. used DRIFTS, XRPD, solid-state NMR spectroscopy and DSC to gain insight into solid-state transformations of ranitidine hydrochloride form I upon milling at different temperatures.[109] Milling at 4°C led to the formation of amorphous ranitidine whereas milling at higher temperatures resulted in ranitidine hydrochloride form II that had formed via amorphous ranitidine. Cheng and colleagues used IR microspectroscopy to show that humidity affected the polymorphic transformation behaviour of famotidine during milling.[110] The study complemented an earlier Raman microscopy study on famotidine that was milled and subsequently heated.[111] Bauer-Brandl and colleagues investigated the behaviour of different solid-state forms of cimetidine during various operations and processes, including heating, milling, exposure to water, tableting and dry storage, which is an important step to find the most suitable solid-state form for the production of solid dosage forms.[112]

Recently, temperature-dependent TPS has been introduced into solid-state analysis. The first study to use temperature-dependent TPS for pharmaceutical analysis characterised the reversible solid-state transformation of carbamazepine form III to form I at various temperatures and at isothermal conditions below the melting point of carbamazepine.[75] TPS showed potential to detect rapid solid-state changes and the mechanism of the solid-state transformation (Figure 2). In a similar study, the five known polymorphs of sulfathiazole and their solid-state conversions upon heating were characterised using variable-temperature TPS and low-frequency Raman spectroscopy.[113] The terahertz spectra of all polymorphic forms were found to be distinct. Upadhya and colleagues studied the different solid-state forms of theophylline and characterised solid–solid transformations of anhydrous theophylline between 4 K up to 523 K using terahertz time-domain spectroscopy.[114] In all three studies, a detailed interpretation of the spectral changes that occurred during conversion of the respective API was difficult since the phonon modes and hydrogen-bonding vibrations recorded in the terahertz spectra could not be assigned to specific molecular structures because of the general lack of knowledge about interpreting bands in terahertz spectra.

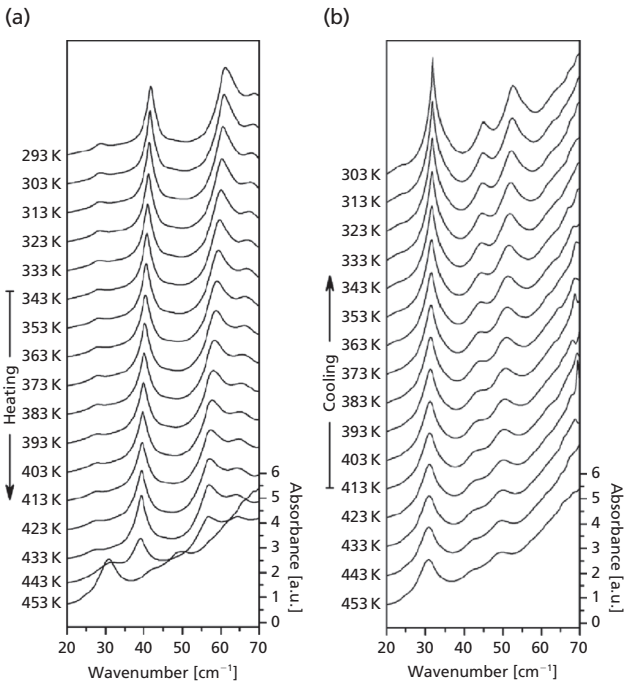

Figure 2 Terahertz absorption spectra of carbamazepine form III during temperature dependent terahertz pulsed spectroscopy measurements. The plots are offset in absorbance for clarity. During heating (a) the transformation from carbamazepine form III to form I takes place. (b) shows the cooling of carbamazepine form I. Reprinted from Zeitler *et al*.[75] with permission from Elsevier.

Solvates

The applications of vibrational spectroscopy to study solvate transformations are summarised in Table 4. Two drugs that have been studied extensively with respect to hydrate formation are theophylline and carbamazepine. The rapid transformation of anhydrous theophylline to theophylline monohydrate during pelletisation upon contact with water[115] and during storage of theophylline tablets[116,117] has been observed. The state of water during transformation of anhydrous theophylline to theophylline monohydrate upon wet granulation in a planetary mixer has been investigated using FT-NIR spectroscopy.[118] The second derivatives of the NIR spectra were analysed and the different states of water in the granules were successfully studied. In a similar study, the hydrate formation of

Table 4 Applications of vibrational spectroscopy to study solid-state transformations of pharmaceutical solvates

API	Phase conversion and mechanism of conversion	Experimental	Spectroscopic technique
Theophylline[118,120]	Solution-mediated hydrate formation to theophylline monohydrate	Wet granulation	NIR spectroscopy
			NIR and Raman spectroscopy
Theophylline, caffeine[119]	Solution-mediated hydrate formation to theophylline monohydrate and caffeine hydrate	Wet granulation	NIR and Raman spectroscopy
Theophylline, nitrofurantoin[121]	Solution-mediated hydrate formation to theophylline monohydrate and nitrofurantoin monohydrate	Channel flow dissolution cell	In-situ Raman spectroscopy
Theophylline[122]	Solution-mediated hydrate formation to theophylline monohydrate	Channel flow dissolution cell and rotating disc apparatus	In-situ Raman spectroscopy
Theophylline[123]	Hydrate formation to theophylline monohydrate, dehydration	Dynamic vapour sorption apparatus	NIR spectroscopy
Theophylline[124]	Solution-mediated hydrate formation to theophylline monohydrate, dehydration	Humidity cell	Raman spectroscopy
Carbamazepine[125,126]	Solution-mediated hydrate formation to carbamazepine dihydrate	Crystalline polymorphs dispersed in water and solid-state conversions measured	Raman spectroscopy
		Crystalline polymorph in ethanol/water mixtures	Raman spectroscopy
Baclofen[127]	Solution-mediated hydrate formation to baclofen monohydrate	Wet granulation	Raman spectroscopy
Azithromycin[49]	Hydrate formation to azithromycin monohydrate and dihydrate	Storage experiments in a desiccator or humidity cell	NIR spectroscopy
Caffeine[128]	Hydrate formation to a non-stoichiometric hydrate of caffeine, dehydrate formation	Humidity cell	NIR spectroscopy
Risedronate sodium[129]	Dehydrate formation of risedronate sodium hemi-pentahydrate	Fluid-bed drying	Raman spectroscopy
Theophylline[130]	Dehydrate formation of theophylline monohydrate	Fluid-bed drying	NIR and Raman spectroscopy
Carbamazepine, piroxicam[131]	Dehydrate formation of carbamazepine dihydrate and piroxicam monohydrate	Fluid-bed drying and experiments on a hot stage	In-situ NIR and Raman spectroscopy
Erythromycin A[132–134]	Dehydrate formation of erythromycin A dihydrate	Fluid-bed drying	In-line NIR spectroscopy
		Fluid-bed drying	At-line NIR spectroscopy
		Hot stage	Hot-stage Raman spectroscopy
Piroxicam[82,135]	Dehydrate formation of piroxicam monohydrate	Hot stage	Hot-stage Raman and NIR spectroscopy
			TPS, NIR and Raman spectroscopy
Lisinopril[136]	Dehydrate formation of lisinopril dihydrate	Hot stage	In-situ IR spectroscopy
Lactose, piroxicam, carbamazepine, theophylline[81]	Dehydrate formation of lactose α-monohydrate piroxicam monohydrate, carbamazepine dihydrate and theophylline dihydrate	Hot stage	In-situ TPS
Ampicillin, nitrofurantoin, besylate salt of compound A[137]	Hydrate formation	Storage	IR spectroscopy
Niclosamide[138]	Hydrate and dehydrate formation	Humidity cell	Raman spectroscopy

API, active pharmaceutical ingredient; IR, infrared; NIR, near infrared; TPS, terahertz pulsed spectroscopy.

theophylline and caffeine during wet granulation in a planetary mixer was followed using off-line charged coupled device Raman and NIR spectroscopy.[119] Furthermore, at-line NIR spectroscopy combined with PCA was used to investigate the effect of water addition during granulation. Raman spectroscopy and NIR spectroscopy were complementary and could be used together to comprehensively describe hydrate formation processes. While Raman spectroscopy was sensitive towards structural changes in the API molecule itself upon hydrate formation, NIR spectroscopy could detect different states of water, including hydrate crystal water and free water. Moreover, NIR spectroscopy and PCA proved to be excellent tools to visualise changes in the state of water during wet granulation.

In addition to the off-line and at-line approaches described above, in-line Raman spectroscopy and univariate analysis, as well as in-line NIR spectroscopy with PLS regression, were used to probe the solid-state transformation to theophylline monohydrate during high-shear wet granulation.[120] It was not possible to follow the transformation kinetics of hydrate formation using NIR spectroscopy because the absorbance of bulk water obscured all spectral information related to the solid-state conversion. In-line Raman spectroscopy, however, provided information about the kinetics of the transformation to theophylline monohydrate. In a study that provided direct evidence of the effect of solid-state conversions on dissolution behaviour, in-line Raman spectroscopy was combined with a channel flow dissolution cell where powder compacts of the API were exposed to the dissolution medium.[121] The kinetics of theophylline and nitrofurantoin hydrate formation were studied quantitatively. In a subsequent study, the transformation from the theophylline anhydrate to the monohydrate during intrinsic dissolution testing was also studied in a rotating disc setup, using simulated gastric fluid (pH 1.2) as the dissolution medium. In addition to different dissolution behaviour, very different monohydrate formation kinetics were observed for the two setups, with the rotating disc setup exhibiting a much slower onset and maximum conversion rate.[122]

Both hydrate formation and dehydration of theophylline were the subject of two recent studies. One investigation employed a combination of dynamic vapour sorption (DVS) and on-line NIR spectroscopy to elucidate the mechanisms of hydrate formation and dehydration of theophylline.[123] The other group used FT Raman spectroscopy combined with a univariate data analysis for quantification.[124] Vora *et al.* used on-line NIR spectroscopy to monitor the solid-state transitions and correlate them with the mass changes recorded by the DVS apparatus during hydrate formation and dehydration.[123] Overall, the combination of DVS and NIR spectroscopy provided insight into the mechanisms of hydrate formation and dehydration of theophylline and revealed the existence of another solid-state form: theophylline dehydrate. Amado *et al.* described the hydrate formation of theophylline at different relative humidities and the dehydration at different temperatures using Raman spectroscopy and univariate analysis. The authors concluded that there is a need for controlled storage conditions to prevent undesired solid-state transformations.[124]

Another drug that has been extensively studied is the anticonvulsant carbamazepine. The solution-mediated conversion of the three known polymorphic forms of carbamazepine to carbamazepine dihydrate was studied using XRPD, scanning electron microscopy and FT-Raman spectroscopy combined with PLS regression.[125] Each form converted to the dihydrate following first-order kinetics, and the crystal morphology was found to have a significant impact on the hydrate formation kinetics, with prisms converting to the dihydrate slower than rods. These results showed the importance of surface properties during solution-mediated solid-state conversions.[125] A similar study has characterised the solution-mediated transformation of carbamazepine anhydrate form III to dihydrate in ethanol/water mixtures at different solvent concentrations and temperatures using in-line Raman spectroscopy.[126] The transformation was found to be a two-step mechanism consisting of the solution of carbamazepine form III and crystallisation of the dihydrate.

Other hydrate formation studies characterised the solid-state behaviour of baclofen during wet granulation experiments using a range of analytical techniques, including FTIR, NIR and Raman spectroscopy,[127] and conversions between different solid-state forms of azithromycin, including the amorphous and hydrate forms, at different relative humidities using NIR spectroscopy and PLS regression.[49] NIR spectroscopy has also been used to study the influence of time, temperature and humidity on interconversions of the anhydrate/hydrate system of caffeine.[128] Phase boundaries at which minimal conversion between the anhydrous and hydrated form of caffeine occurred were identified from the kinetic data. Overall, it was found that quantitative NIR spectroscopy can be used to rapidly determine the stability of solvatomorphs as well as the kinetics of solid-state transformations.

In addition to monitoring hydrate formation processes of APIs, it is crucial to monitor dehydration processes associated with drying or compaction steps during pharmaceutical manufacturing. Fluid-bed drying, for instance, is typically used to remove bulk water from the granules after wet granulation. Incomplete drying may lead to the formation of an unstable product in a non-equilibrium hydration state, which is why the drying process, including its endpoint, needs to be carefully monitored. The dehydration behaviour of risedronate sodium hydrate, a mixed hydrate containing both channel and crystal lattice water, upon fluid-bed drying was investigated using on-line Raman spectroscopy.[129] It was found that the final moisture content of the granules influenced the compression behaviour of the system and the physical stability of the tablets produced from these granules. In similar studies, the isothermal dehydration of theophylline monohydrate and carbamazepine dihydrate was characterised and quantified during fluid-bed drying using on-line Raman spectroscopy and on-line NIR spectroscopy combined with PLS regression. A microscale fluid-bed dryer was used to dry granules of theophylline monohydrate at two different temperatures.[130] PLS analysis of the spectroscopic data revealed that NIR spectroscopy and Raman spectroscopy provided complementary information about the dehydration process: NIR spectroscopy was sensitive to the decrease in the water content of the granules that occurred almost immediately after the start of the fluidisation, whereas Raman spectroscopy was able to detect changes in molecular packing that started with a short lag time after the beginning of the fluidisation, when some water had already evaporated.

Kogermann and colleagues developed quantification models to monitor different solid-state forms occurring during dehydration of carbamazepine dihydrate and piroxicam monohydrate *in situ* on a hot stage as well as during fluid-bed drying.[131] In agreement with the study performed by Aaltonen *et al*., Raman spectroscopy was found to be more sensitive to structural changes between the different solid-state forms of the two APIs during dehydration, whereas NIR spectroscopy detected predominantly changes in the water content.[130] Further dehydration studies characterised the phase transformations of erythromycin A during fluid-bed drying of pellets containing erythromycin and microcrystalline cellulose by in-line NIR spectroscopy and PCA[132] and during pellet manufacturing by at-line NIR spectroscopy.[133] The mechanism of the dehydration could be described and the existence of erythromycin dehydrate, an isomorphic structure to erythromycin dihydrate, was confirmed as a result of the loss of two molecules of water from each erythromycin molecule. NIR spectroscopy combined with PCA was found to be suitable for endpoint control during pharmaceutical manufacturing.

While the aforementioned studies described dehydration processes for drying steps during pharmaceutical manufacturing, other groups have investigated dehydration processes on hot stages. The thermally induced dehydration of erythromycin A dihydrate, for instance, was characterised using variable-temperature XRPD and hot-stage Raman spectroscopy, which proved to be a suitable tool for structural interpretation of solid-state changes during dehydration.[134] In another work, the isothermal dehydration of piroxicam monohydrate and carbamazepine dihydrate was studied at different temperatures using hot-stage NIR and Raman spectroscopy combined with PLS discriminant analysis (PLS-DA) to qualitatively describe the solid-state transformations.[135] The PLS-DA models for NIR and Raman spectroscopy were constructed on the basis of the spectra of the pure solid-state forms of carbamazepine and piroxicam. In-situ monitoring of dehydration revealed insight into the dehydration processes and multiple solid-state forms that occur upon dehydration of carbamazepine dihydrate, while the removal of water from piroxicam monohydrate led to the formation of only crystalline form I (Figure 3). The same group conducted a similar study in which they monitored the isothermal and non-isothermal dehydration of piroxicam monohydrate from compacts using in-situ TPS, NIR and Raman spectroscopy using PCA.[82] All three spectroscopic techniques combined with PCA were found to be suitable for monitoring solid-state transformations and provided complementary information: Raman spectroscopy and TPS allowed the detection of structural changes in the piroxicam molecules, and NIR spectroscopy detected changes in the water content during dehydration. Mid-IR spectroscopy, which is sensitive to both solid-state form and the presence of water, was used to analyse drug dehydration on a hot stage using a microscope setup in transmission mode. A different multivariate method – self-modelling curve resolution – was used to quantify multiple forms of lisinopril during its dehydration.[136] Another recent study using variable-temperature TPS investigated differences in the terahertz spectra of anhydrous and hydrated APIs, including lactose, piroxicam, carbamazepine and theophylline, and also analysed the dehydration of theophylline monohydrate *in situ* between 293 and 437 K.[81] The anhydrous and hydrated forms of the different APIs could be easily distinguished using TPS. The dehydration experiment on theophylline monohydrate revealed that in-situ TPS is a valuable technique for studying dehydration and water evaporation processes and mechanisms in pharmaceutical materials.

Vibrational spectroscopy has great potential for qualitative and quantitative analysis of dehydration and hydrate formation during storage studies. Kojima and colleagues found that DRIFTS, which is sensitive to hydrogen bonding between water and drug molecules, could detect initial hydrate formation of some APIs before XRPD.[137] Sardo *et al*. used Raman spectroscopy and spectral deconvolution of selected bands to quantify the dehydration and hydrate formation of niclosamide stored at different humidities.[138] Vibrational spectroscopy is expected to become widely used during storage studies of both APIs and final dosage forms.

Amorphous forms

Solid-state conversions from crystalline to amorphous forms of APIs have been qualitatively or even quantitatively observed during several pharmaceutical processes such as milling, wet granulation and freeze-drying (Table 5). The formation of amorphous lactose upon milling of α-lactose monohydrate and the increase in the amorphous content in the crystalline samples, for instance, was quantified using on-line Raman and NIR spectroscopy combined with PLS regression.[47] This study showed that these techniques allowed rapid and non-invasive monitoring of solid-state transformations during pharmaceutical manufacturing. In another work, solid-state transformations, including amorphisation during wet granulation, were described for the API Abbott-232 using a range of analytical methods including XRPD, polarising light microscopy, DSC, thermogravimetric analysis and Raman spectroscopy.[139] The amorphisation of paracetamol in polymeric mixtures containing the drug and microcrystalline cellulose, hydroxypropyl methylcellulose or cross-linked polyvinyl pyrrolidone after melting and cooling has been observed using a range of techniques, including DSC, hot-stage microscopy, micro FTIR spectroscopy and scanning electron microscopy.[140] The two studies confirmed the potential of spectroscopic techniques to detect and characterise solid-state transformations. A pressure-induced amorphisation of indometacin was observed in a study that aimed to establish a PLS method to determine the microcrystallinity of indometacin in model compacts of indometacin and mannitol based on Raman spectroscopy.[141] Crystalline indometacin was found to undergo a conversion to amorphous indometacin, which was more pronounced at higher compaction pressures. Furthermore, differences in microcrystallinity of indometacin at the surface and the interior of the compact could be described and showed the value of the Raman spectroscopic PLS model. In a storage study, Raman spectroscopy was combined with XRPD to qualitatively analyse the spontaneous loss of crystallinity of various drugs in partially crystalline polyethylene oxide matrices stored at high humidity. The degree of crystallinity loss was related to the ability of each drug to dissolve in regions where the amorphous polymer and water

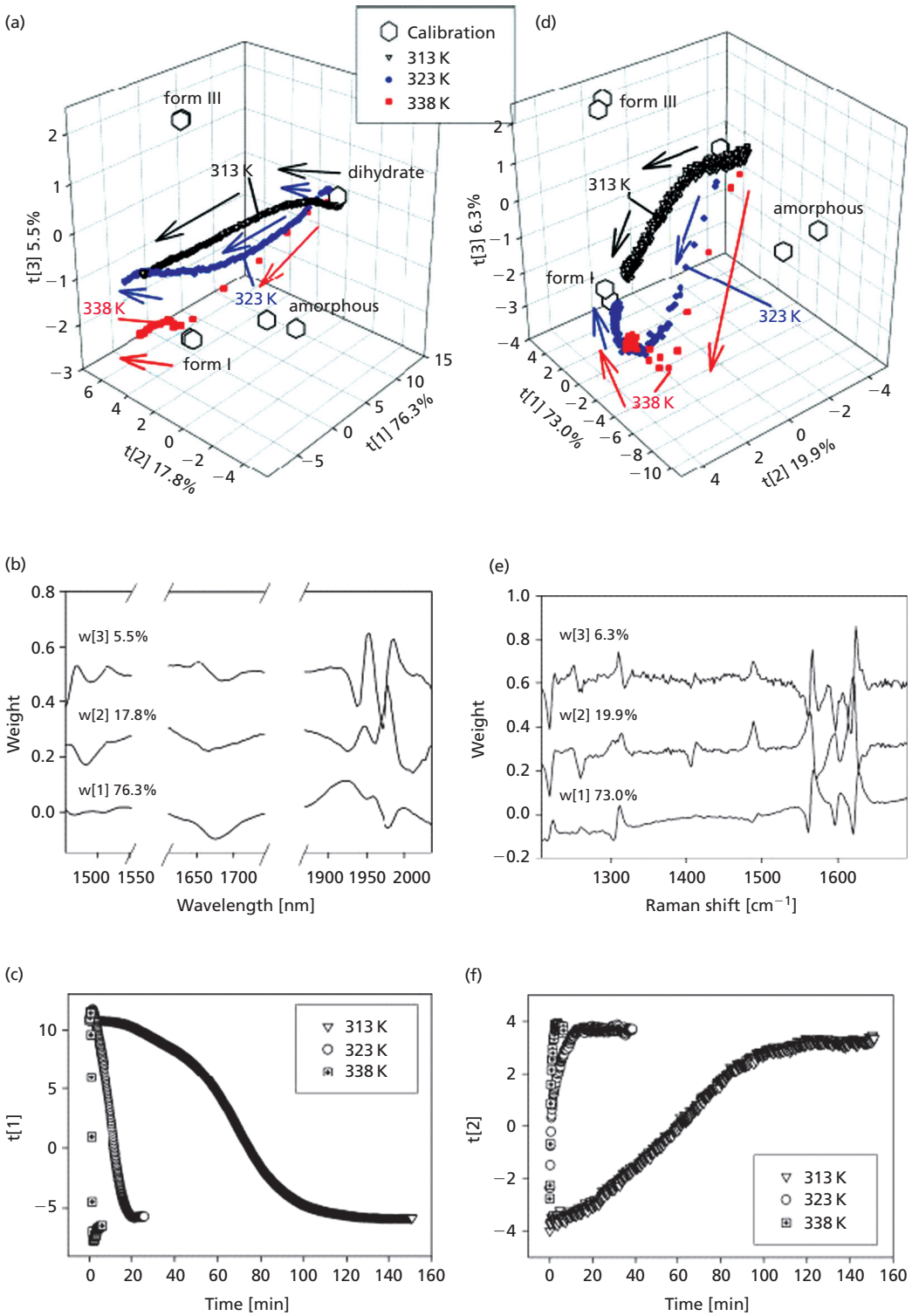

Figure 3 Model construction and isothermal dehydration of carbamazepine dihydrate. (a) Score values of near-infrared (NIR) spectra for the first, second and third components and projections of hot-stage measurements at different temperatures. (b) Weight vectors of the NIR partial least-squares discriminant analysis (PLS-DA) model (weights of second and third are offset for clarity). (c) Score values for the first component of the NIR spectra versus time for dehydration of carbamazepine dihydrate at different temperatures. (d) Score values of Raman spectra for the first, second and third components and projections of hot-stage measurements at different temperatures. (e) weight vectors of the Raman PLS-DA model (weights of second and third components are offset for clarity). (f) Score values for the second component of the Raman spectra versus time for dehydration of carbamazepine dihydrate at different temperatures. Arrows point out the direction of dehydration; different temperatures are labelled with numbers and different colours. Reprinted from Kogermann *et al.*[135] with permission from Wiley.

Table 5 Applications of vibrational spectroscopy to study solid-state transformations of amorphous systems

API	Phase conversion and mechanism of conversion	Experimental	Spectroscopic technique
Lactose, trehalose[47]	Amorphisation of lactose and recrystallisation of amorphous lactose and amorphous trehalose	Solid-state conversion induced by milling	NIR and Raman spectroscopy
Abbott-232[139]	Amorphisation after dissolution and drying of anhydrous Abbott-232	Wet granulation and subsequent drying	Raman spectroscopy
Paracetamol[140]	Amorphisation and recrystallisation	Melting and cooling API–polymer mixtures	Micro FTIR spectroscopy
Indometacin[141]	Solid–solid amorphisation of crystalline indometacin to amorphous indometacin	Solid-state conversion induced by pressure	Raman spectroscopy
Paracetamol, ketoprofen, naproxen, ibuprofen[142]	Amorphisation in polyethylene oxide matrices at high humidity	Storage at high humidity (94% RH) in room temperature	Raman spectroscopy
Nifedipine[143]	Recrystallisation of amorphous nifedipine via metastable β-form to α-nifedipine	Different relative humidities	In-situ FTIR and Raman microscopy
Carbamazepine[144]	Solid–solid recrystallisation of amorphous carbamazepine to carbamazepine form III	Heating	In-situ TPS
Fenofibrate[145]	Solid–solid recrystallisation of amorphous fenofibrate via metastable form II to form I	Heating	In-situ Raman spectroscopy
Carbamazepine, indometacin[146]	Solution-mediated recrystallisation of amorphous indometacin and carbamazepine	Dissolution experiment	In-situ Raman spectroscopy

API, active pharmaceutical ingredient; FTIR, Fourier transform infrared; IR, infrared; NIR, near infrared; RH, relative humidity; TPS, terahertz pulsed spectroscopy.

coexisted as 'co-solvents'.[142] Such behaviour may prevent analysis of accelerated stability studies using Arrhenius extrapolations.

A few recrystallisation studies have used in-situ vibrational spectroscopy to monitor and characterise multiple solid–solid transformations during recrystallisation of amorphous APIs. For example, in-situ IR and Raman spectroscopy were used to study the recrystallisation of amorphous nifedipine in a controlled humidity cell at different relative humidities.[143] Increasing the relative humidity decreased the recrystallisation onset time. The authors concluded that in-situ IR and Raman microscopy are useful tools to examine environmental effects on the solid state of an API. In another study, in-situ variable-temperature TPS was used to study the recrystallisation of carbamazepine produced by quench-cooling a melt of polycrystalline carbamazepine.[144] When the amorphous material was heated, the transition from the glassy to the rubbery state could be observed, as well as the recrystallisation to form III and eventually form I. In another study, a combination of in-situ variable-temperature Raman spectroscopy, computational chemistry and PCA was used to investigate the recrystallisation pathway of amorphous fenofibrate.[145] Amorphous fenofibrate was found to crystallise to its stable form I via the metastable form II, whose existence could be confirmed by Raman spectroscopy and PCA (Figure 4). The solvent-mediated solid-state conversions that occur during dissolution of amorphous indometacin and amorphous carbamazepine were monitored and quantified using a combination of in-situ Raman spectroscopy with multivariate approaches – either PLS-DA or PLS regression.[146] The dissolution experiments with amorphous indometacin and amorphous carbamazepine were carried out in a channel flow intrinsic dissolution test apparatus. Raman spectroscopy combined with PLS-DA was found to be more sensitive to the solid-state changes than XRPD, which was used as an additional technique to analyse solid-state changes.

Conclusions

In the last decade, vibrational spectroscopic techniques including IR, NIR, Raman spectroscopy and, more recently, TPS have become popular for detecting, characterising and monitoring solid-state transformations. Studies have focused on solid-state conversions that occur during various steps of pharmaceutical manufacturing such as crystallisation, wet granulation, milling, freeze-drying, spray-drying and tableting, and have tried to shed light on the mechanism and kinetics of the transformations as well as factors that influence the conversions. In this context, vibrational spectroscopy has several advantages over other commonly used analytical methods, including thermal techniques and XRPD. Vibrational spectroscopic techniques are fast and non-destructive, and the development of new sampling accessories and setups, such as the growing use of fibreoptic probes, has extended the possibility of using vibrational spectroscopy in diverse environments encountered throughout the lifecycle of pharmaceutical APIs and their products.

When used with sophisticated data analysis approaches, the sensitivity and selectivity of solid-state spectroscopy has increased and allowed on-line analysis of solid-state transformations and routine quality control during pharmaceutical processing. Of all vibrational spectroscopic techniques, NIR spectroscopy has dominated the field of process analytical technology in the last years, since no sample preparation is required, fibreoptic probes can be used routinely and hence processes are easily monitored in-line. Even though the analysis of NIR spectra is rather challenging because of overtone and combination bands that often cannot be

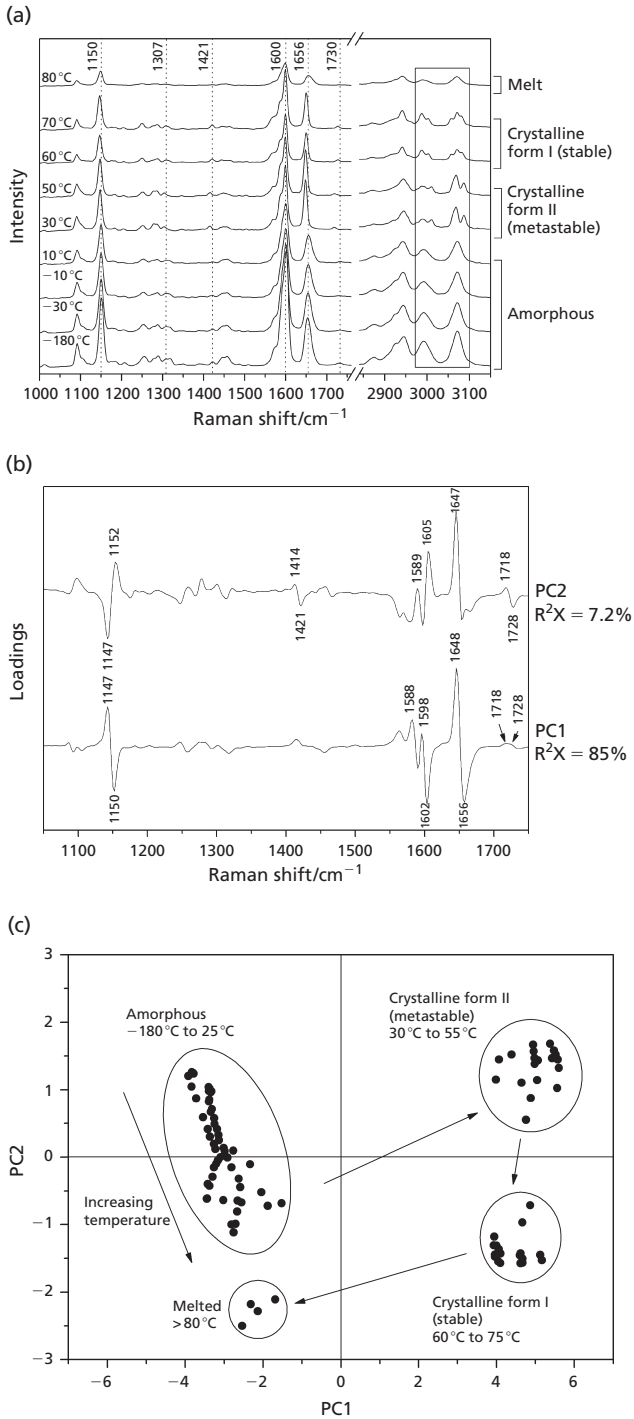

Figure 4 Solid-state transformations of amorphous fenofibrate upon heating. (a) Selected Raman spectra showing the recrystallisation behaviour of amorphous fenofibrate between −180 and 80°C. (b) Loadings and (c) scores plots generated by principal component analysis from the Raman spectra obtained upon heating amorphous fenofibrate between −180 and 90°C. Loadings are offset for clarity. Reprinted from Heinz *et al.*[145] with permission from Elsevier.

specifically assigned to molecular vibrations, studies have shown that NIR spectroscopy is most suitable for the analysis of hydrate formation and dehydration processes, since the technique can identify different states of water in solid samples. Furthermore, in-line Raman spectroscopy has become a powerful method for process analytical purposes in aqueous sampling environments where NIR spectroscopic analysis fails because significant spectral bands are obscured by water bands. Raman spectroscopy provides complementary structural information to both NIR and IR spectroscopy. The use of IR spectroscopy is still mainly limited to off-line analysis of solid-state transformations since probes are not yet used routinely. IR spectroscopy is hence often used in combination with other vibrational spectroscopic techniques. Even though terahertz spectra still cannot be fully interpreted, TPS provides extremely useful complementary information to IR and Raman spectroscopy since it probes whole-lattice vibrations. With advances in sampling setups and data interpretation, the use of TPS for solid-state characterisation is likely to expand.

Overall, technical advances in the last years have promoted the use of vibrational spectroscopy for process analytical purposes, including the detection and quantification of solid-state conversions. Various studies have shown the potential benefit of using different vibrational spectroscopic techniques in combination to obtain complementary structural information.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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