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Drug hydrate systems and dehydration processes studied by terahertz pulsed spectroscopy

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Abstract

Terahertz pulsed spectroscopy was used to distinguish between different hydrate systems. In the example of four pharmaceutical materials lactose, carbamazepine, piroxicam and theophylline it was demonstrated that all different hydrate and anhydrate forms exhibit distinct spectra in the far infrared. Furthermore the dehydration of theophylline monohydrate was characterised *in situ*. Here, a phase transition from the monohydrate to the anhydrous form was observed, followed by evaporation of the hydrate water in a second step. The rotational spectrum of water vapour is very characteristic in the far infrared and can easily be discerned from the terahertz spectrum of the solid state form.

Keywords: Terahertz pulsed spectroscopy (TPS); Hydrate forms; Theophylline monohydrate; Dehydration; Phase transition; Principal components analysis

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1. Introduction

It has been estimated that one in every three drug compounds can exist as a hydrated form (Threlfall, 1995). Hydrated forms may have different physicochemical properties to their anhydrous counterparts, and for pharmaceutical development this has therapeutic, manufacturing, legal and commercial implications (Brittain, 1999; Bernstein, 2002). A number of factors may trigger and/or promote hydrate formation, including exposure to water and temperature changes (Airaksinen et al., 2005b). Such conditions frequently occur during dosage form production processes. For example, before or during mixing a drug with excipients for tablet production it is common practice to perform a wet granulation step where the powder blend is granulated into larger particles by aqueous polymer solution to achieve better flow properties. The aggregates must then be dried, using a process such as fluid bed drying. During such processes the drug is very likely to form different hydrate and/or anhydrate forms (Morris et al., 2001; Airaksinen et al., 2005a,b; Aaltonen et al., 2006). Hydrate formation in tablets stored in ambient conditions, especially in dosage forms that contain excipients with loosely bound water, such as starch or cellulose, may also occur. Therapeutic failure has been attributed to this phenomenon highlighting the importance to understand the hydration behaviour of drug materials (Meyer et al., 1992).

Hydrate forms of drugs have been classified into three different categories according to the distribution of water within their crystal lattice: channel, isolated-site and ion-bound hydrates (Morris, 1999). These classes are postulated to exhibit different solid state transformation mechanisms, though such mechanisms and the consequences thereof are poorly understood at present. To control the solid state properties of materials

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during dosage form production, it is imperative to obtain a molecular level understanding of dehydration and hydration processes.

Among other techniques such as thermal analysis and X-ray powder diffraction (XRPD), spectroscopic methods have been increasingly used to characterise hydrate/anhydrate systems. There are a number of advantages for using spectroscopic techniques to analyse these systems. The spectra directly reflect inter- and intramolecular properties, and therefore provide a tool to understand hydration and dehydration processes at a molecular level. In addition, spectroscopic techniques are non-destructive and, with the exception of solid state NMR, very rapid compared to conventional methods. Some of the techniques have the potential to study hydrate or anhydrate formation and dehydration in real time during production processes. Terahertz pulsed spectroscopy (TPS) has recently been demonstrated to be an interesting novel technique for the investigation of solid state properties in pharmaceutical materials and products (Taday et al., 2003; Strachan et al., 2004, 2005; Zeitler et al., 2006). It has been used to monitor polymorphic phase transitions in real time (Zeitler et al., 2005). In recent theoretical studies first approaches were presented for a better interpretation of the spectra which predominantly reflect information on the intermolecular vibrations in the crystalline lattice (Day et al., 2006; Allis et al., 2006).

The purpose of the study is to investigate the differences in the terahertz pulsed spectra of anhydrous and hydrated materials and to evaluate the potential of variable temperature TPS for the characterisation of dehydration processes.

2. Materials and methods

2.1. Materials

Lactose α-monohydrate (αL-H_2O, 4-*O*-D-galactopyranosyl-α-D-glucopyranose monohydrate) was obtained from Fisher Scientific (Loughborough, UK). Carbamazepine (CBZ, 5H-dibenz[*b,f*]azepine-5-carboxamide, USP grade) and piroxicam (PXM, 4-hydroxy-2-methyl-*N*-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide, USP grade) were purchased from Hawkins, Inc. Pharmaceutical Group (Minneapolis, MN, USA). Theophylline (TP, 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione) was obtained from BASF (Ludwigshafen, Germany).

2.2. Sample preparation

The αL-H_2O form was used as received. The unstable α-anhydrate form of lactose (αL_H) was prepared by heating αL-H_2O in a stainless steel Petri dish at 383 K for 6 h (Garnier et al., 2002).

The supplied form of CBZ was polymorph III. To ensure polymorphic purity form III was obtained by dehydration of the dihydrate form under reduced pressure (72 mBar) for 24 h at 373 K. CBZ form I was prepared by heating the raw material for 2 h at 443 K (Lefebvre et al., 1986). The dihydrate was prepared by recrystallization from a hot (353 K) saturated aqueous solution. The solution was cooled slowly to room temperature. After filtration the crystals were dried at ambient conditions and the obtained hydrate forms were stored at 54% RH.

PXM monohydrate was prepared from the raw material (form I) by recrystallization as described for CBZ dihydrate. Samples were stored at 54% RH. Pure form I was obtained by dehydration of the monohydrate (72 mBar, 24 h, 373 K).

The monohydrate form of TP was also produced by recrystallization of the raw anhydrous material and stored at 75% RH prior to the measurements. For the samples of the anhydrate form the monohydrate was dehydrated (72 mBar, 24 h, 373 K).

All anhydrous forms were stored over silica gel at room temperature.

The reference codes in the Cambridge Structural Database (CSD, Cambridge Crystallographic Data Centre, Cambridge, UK) for the respective forms are LACTOS10 (αL-H_2O), CBMZPN01 (CBZ form III), CBMZPN11 (CBZ form I), FEFNOT (CBZ dihydrate), BIYSEH (PXM form I), CIDYAP01 (PXM monohydrate), BAPLOT01 (TP anhydrate) and THEOPH01 (TP monohydrate). For the crystallographic information of αL_H the structure solved by Platteau et al. (2005) based on the powder pattern was used as no single crystal data is available for this modification.

2.3. X-ray powder diffraction

X-ray powder diffraction (XRPD) patterns of all forms were recorded by using a theta–theta diffractometer (Bruker AXS D8 Advance, Bruker AXS GmbH, Karlsruhe, Germany). For the comparison of the recorded patterns to their theoretical diffraction patterns reference data from the CSD was used.

2.4. Terahertz pulsed spectroscopy

Sample material (Table 1) was mixed with polyethylene (PE, Induchem, Volketwil, Switzerland, particle size $< 10\ \mu m$) and subsequently compressed at a load of 2 tonnes into a pellet for the terahertz spectra at room temperature. The thickness of the pellets was between 3.2 mm and 3.4 mm. Spectra were recorded using a TPS spectra1000 V spectrometer (TeraView, Cambridge, UK) with a spectral resolution of $1\ cm^{-1}$ over the range of $2–130\ cm^{-1}$ by co-adding 1800 scans as reported previously (Strachan et al., 2005). Blackman-Harris 3-term apodization was used for the Fourier transformation. Sample spectra were referenced against the spectrum of a PE pellet and absorbance spectra were calculated.

For the acquisition of terahertz spectra at 90 K a variable temperature cell (Specac, Orphington, UK) equipped with z-cut quartz windows was used. The sample was attached to the cold finger of the temperature cell and the cell was evacuated during the measurements. Liquid nitrogen was used to cool the sample to 90 K. Spectra were recorded by co-adding 1800 scans and referenced against a spectrum of PE at 90 K.

The dehydration of TP monohydrate was investigated at elevated temperatures. TP monohydrate (15 mg) was mixed with

Table 1
Amount of sample material used to prepare the pellets for the measurements at 293 K and 90 K after mixing with 360 mg PE

	293 K	90 K
αL_H	15	15
$\alpha L\text{-}H_2O$	15	15
CBZ I	15	20
CBZ III	15	20
CBZ dihydrate	30	20
PXM I	30	15
PXM monohydrate	15	15
TP anhydrate	15	15
TP monohydrate	15	15

poly(tetrafluoroethylene) (PTFE, Aldrich, UK) and compressed into a pellet. *In situ* spectra of TP during heating were acquired using a variable temperature cell (Specac, Orphington, UK) as described previously (Zeitler et al., 2005). The sample pellet was heated at 5 K min^{-1} and terahertz spectra were acquired every 30 s by co-adding 900 scans per spectrum. Absorbance spectra were calculated using a reference spectrum of PTFE. The sample chamber was purged with dry nitrogen gas throughout all measurements. Spectral acquisition and processing was performed using TPI Spectra software (TeraView, Cambridge, UK). The spectral refractive indices of each material at room temperature were calculated directly using the measured terahertz electric field and the sample thickness.

2.5. *Multivariate analysis*

Multivariate analysis of the spectral data acquired for the dehydration of TP was performed by principal components analysis on centred spectral data between 5 cm^{-1} and 110 cm^{-1} (PCA, SIMCA-P, Version 10.5, Umetrics AB, Umeå, Sweden). In PCA the data is decomposed into a new set of variables called principal components (PCs). The PCs are composed of two sets of data: the scores (t) and loadings (p) with the scores referring to spectral variation and the loadings representing the spectral contribution to each PC. The analysis can then be restricted to the first couple of PCs that describe the highest variance in the spectra (Eriksson et al., 1999).

3. Results and discussion

3.1. *Terahertz spectra of different hydrate forms*

The crystal structures of all forms were verified by their XRPD patterns compared to reference powder patterns (data not shown). All forms show distinct differences in their terahertz spectra that allow the hydrate and anhydrate forms to be readily distinguished by their room temperature spectra (Fig. 1 and Table 2). The measured refractive indices of the materials were found to be between 1.6 and 2.3 at room temperature.

Upon cooling the samples to 90 K an increase in intensity of all spectral features can be observed. The peak widths

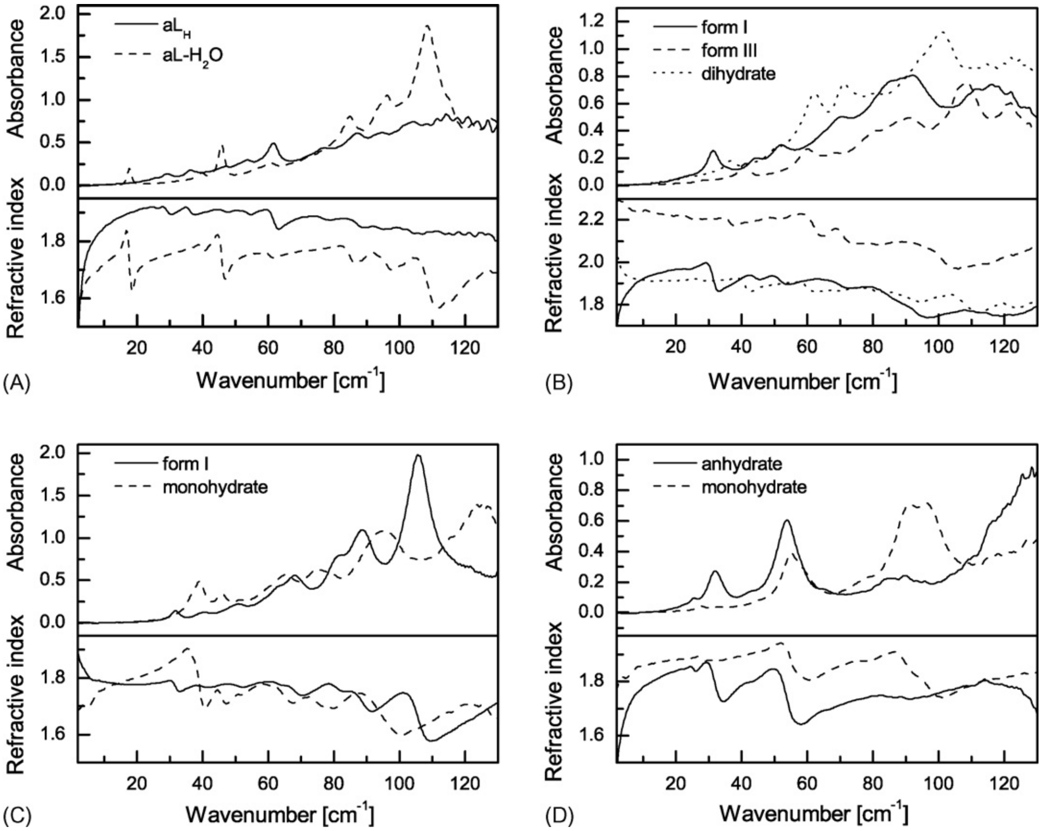

Fig. 1. Terahertz absorption spectra and frequency dependent refractive indices of the different hydrate and anhydrate forms at 293 K. (A) αL_H and $\alpha L\text{-}H_2O$, (B) CBZ forms I, III, and dihydrate, (C) PXM form I and monohydrate, and (D) TP anhydrate and monohydrate.

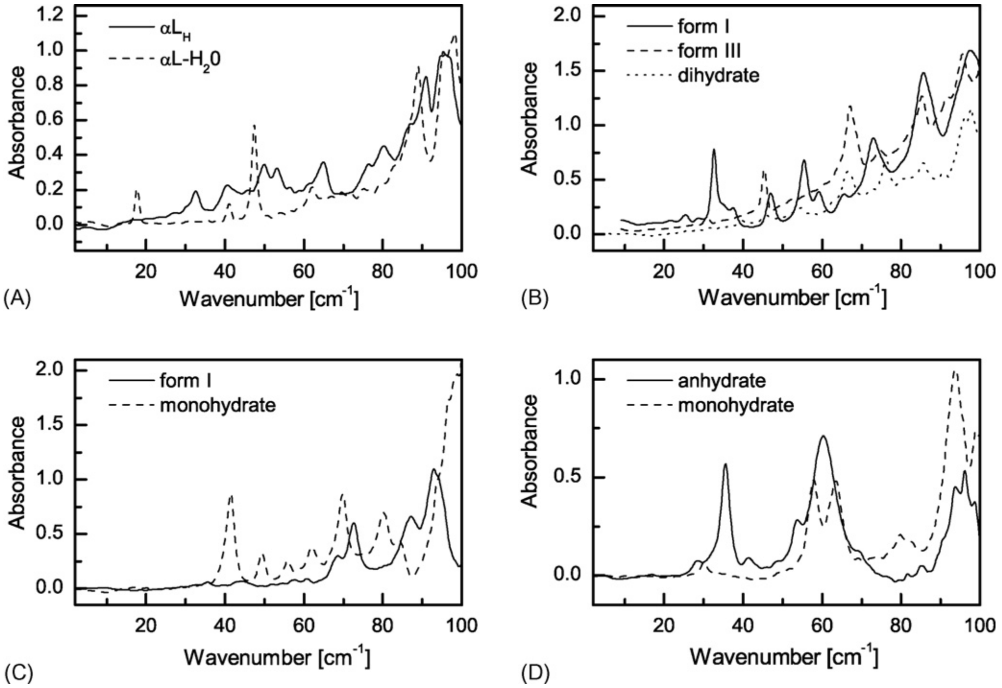

Fig. 2. Terahertz absorption spectra at 90 K for the different hydrate and anhydrate forms. (A) αL_H and αL-H_2O, (B) CBZ forms I, III, and dihydrate, (C) PXM form I and monohydrate, and (D) TH anhydrate and monohydrate.

decrease, the peak positions blue-shift to higher wavenumbers and features that overlap at room temperature resolve (Fig. 2 and Table 2).

No refractive indices were calculated for the terahertz signal at 90 K as it was not possible to measure the thickness of the sample at this temperature. Due to thermal contraction the thickness of the sample pellets would decrease considerably and the absolute value for the spectral refractive indices would not be accurate.

3.2. *In situ dehydration study of theophylline monohydrate*

The dehydration process of TP monohydrate was investigated *in situ*. The monohydrate spectrum at 293 K is dominated by a peak at 55 cm^{-1} with a shoulder at 60 cm^{-1} and a doublet at 92 cm^{-1} and 96 cm^{-1}. Upon heating the sample the spectral features red-shift to lower wavenumbers and decrease in intensity (Fig. 3).

At 350 K two narrow spectral features start to increase in intensity in the spectrum of TP monohydrate at 88 cm^{-1} and 93 cm^{-1}. These features correspond to two of the rotational transitions in the terahertz spectrum of water vapour. With the acquisition parameters used for these terahertz measurements the narrow lines of the rotational spectrum of water vapour are under-resolved by orders of magnitude. However, even at a spectral resolution of 1 cm^{-1} and after applying Blackman–Harris apodisation during the Fourier transformation, the spectrum of water vapour is still very distinct and reproducible (see inset in Fig. 3). As the sample chamber is carefully purged with dry nitrogen throughout the measurements, the presence of water vapour in the spectra indicates the evaporation of hydrate water from the molecular crystal.

Although only two out of the numerous spectral features of water vapour can be observed at this temperature, the doublet in the TP monohydrate spectrum can no longer be discerned in the presence of the water vapour signature. A general increase in absorbance at higher wavenumbers leads to a further decrease in signal-to-noise ratio and the spectra therefore become noisier at higher wavenumbers.

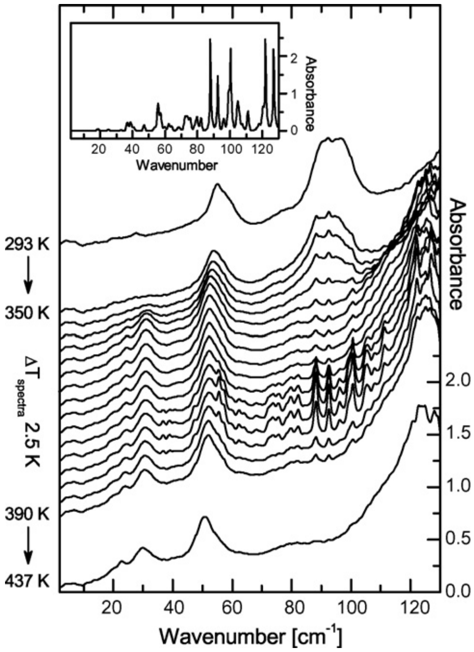

Fig. 3. Terahertz absorption spectra of TP monohydrate during heating from 293 K to 437 K. The spectra are offset in absorbance for clarity. The inset shows the terahertz spectrum of water vapour recorded with the same acquisition parameters as for the variable temperature measurements.

Table 2
Positions of spectral features for the different hydrate forms in the terahertz spectra at 293 K and 90 K

	293 K	90 K
αL_H	$30_w, 36_w, 47_w, 54_w, 62, 76_w, 87_w, 94_w, 104_w$	33, 41, (50, 53), 65, 76_w, 80, 91, 96
αL-H_2O	18, 40, 46, 60, 85, 96, 108	18, 41, 47, 62, 89
CBZ form III	$28_w, 41, 60, 68_w, 80_w, 88_s, 91, 105_s, 109, 122$	$31_w, 45, 67, 75_w, 85, 96$
CBZ form I	31, 44_w, 52, 60_w, (85, 93), (111, 116, 122)	$25_w, 29_w, 33, 35_s, 37_w, 47, 55, 59_w, 66_w, 73, 86, 97$
CBZ dihydrate	$39_w, 51_s, 62, 71, 80_w, 101$	$39_w, 46_w, 55_w, 63_s, 67, 73_w, 76, 81_w, 86, 91, 98$
PXM form I	$32, 40_w, 50_w, 63_s, 68, 81_s, 89, 106$	$36_w, 44_w, 58_w, 61_w, 69, 73, 87, 93$
PXM monohydrate	$39, 46, 52_w, 65, 75, 96, 125$	$41, 49, 56, 62, 70, 75_w, 80, 84$
TP anhydrate	$25_w, 32, 43_w, 54, 65_{w,s}, 90$	$28_w, 36, 41_w, 48_w, 54, 60, 70_s, 82_w, 85_w, 96$
TP monohydrate	28_w, 55, 59_s, 77_s, (91, 96)	$30_w, 52_s, 58, 64, 69_w, 74_w, 80, 82_s, 94$

Parenthesis refer to unresolved spectral features, w denotes a weak feature and s a shoulder.

An additional broad peak starts to emerge at 32 cm^{-1} in the spectrum at 355 K. At the same time the intensity of the initial doublet decreases drastically and the peak at 55 cm^{-1} shifts to 53 cm^{-1} indicating a phase transition of the monohydrate crystal structure to the crystal structure of the anhydrous form. This observation corresponds very well to studies by thermal analysis (Suihko et al., 1997). An intermediate metastable anhydrous form of TP upon dehydration has been reported (Phadnis and Suryanarayanan, 1997). There are no features in the terahertz spectra that suggest that this metastable form occurred. It is possible that this form is occurring at concentrations that are not detectable. However, it has also been noted that the dehydration behaviour of TP is considerably different in open and closed systems (Suihko et al., 1997), with the reported metastable form being observed under open conditions. Compression of the TP into a hydrophobic matrix of PTFE can be considered closer to a closed system, since the water cannot freely escape the sample. This may explain the apparent absence of the metastable form upon dehydration in the terahertz spectra. Further heating to 360 K leads to an additional peak at 25 cm^{-1}. Another sharp peak 100 cm^{-1} due to water vapour appears. The intensity of the three water vapour features remains weak but constant during further heating.

This observation changes at 375–378 K. The intensity of the three rotational spectral features increase strongly and nearly all other peaks of the water vapour spectrum appear superimposed onto the TP anhydrate spectrum at 378 K. For the next 120 s the spectral signature of water vapour is very dominant until the temperature has reached 388 K. From then onwards the intensity of the water vapour signal decreases rapidly and in the spectrum at 437 K all water vapour features disappear.

In the contour plot of the variable temperature experiment (Fig. 4) the peak shifts, phase transition and hydrate water evaporation can be followed in more detail. The dehydration process in this sample (a compressed pellet) is clearly a two step process, with a phase transition and the water evaporation in a second step. The time lag between the phase transition and the evaporation step is likely to result from the water vapour diffusion through the PTFE matrix. The dehydration experiment was found to be reproducible.

Recently, Upadhya et al. (2006) have reported the terahertz spectra of two different anhydrous modifications and the monohydrate of TP. The spectra that have been presented for one of the anhydrous forms (called form II in the work by Upadhya et al. (2006)) and of the monohydrate match the spectra in Fig. 1. The other anhydrous form (called form I) was prepared by heating form II to 523 K and keeping it isothermal for 5 h. This is likely to be the form prepared under similar conditions by Suzuki et al. (1989), and is different to the metastable form observed by Phadnis and Suryanarayanan (1997) and Vora et al. (2004). A study of the phase transition between the monohydrate and form II and between form II and form I was performed but the samples were not measured *in situ*. For each terahertz spectrum during the phase transition a sample of the material was heated for a certain time, allowed to cool and then a pellet was prepared using the heat treated material. With this approach it was possible to describe the overall phase transition from the monohydrate to the anhydrate (form II). However, the second step of this process involving the evaporation of the hydrate water (see Fig. 3) could not be detected. The observation of this step requires the process to be monitored *in situ* as the event of water evaporation is transient and intrinsically tied to the temperature of the sample. Even though in the work by Upadhya et al. (2006) the powder of TP monohydrate is heated rather than the compressed pellet there is no indication of a metastable form of TP as described by Phadnis and Suryanarayanan (1997). It is possible that the metastable form, once formed during the dehydration, converts back into the stable anhydrate during the preparation of the sample pellet. To confirm the formation of the metastable form during dehydration it would therefore be necessary to acquire *in situ* spectra of a sample of TP monohydrate in powder form rather than in a pellet.

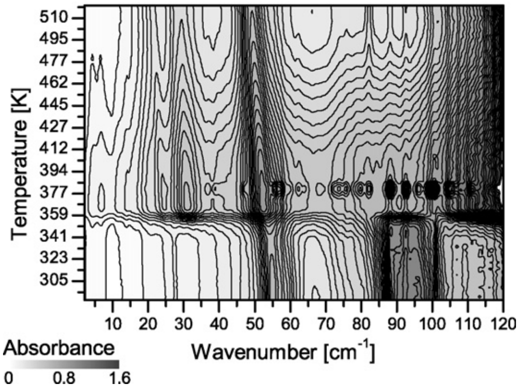

Fig. 4. Contour plot of the terahertz spectra during dehydration of TP monohydrate.

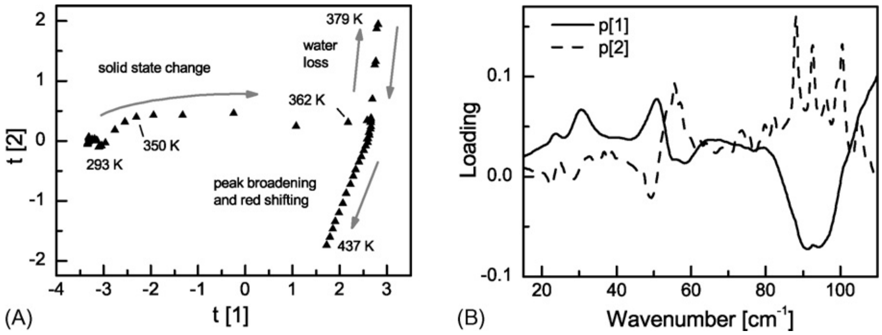

Fig. 5. PCA plots of TP monohydrate during heating. (A) Scores for first and second components (*t*[1] and *t*[2]). (B) Loadings of the first and second components (*p*[1] and *p*[2]).

PCA was used to further investigate the variable temperature experiment (Jørgensen et al., 2006). The first PC represented 92.7% of the spectral variation, the second, 5.7%. The first and second scores (*t*[1] and *t*[2], respectively, Fig. 5A) do not change until the sample reaches 343 K. At this point a large increase in *t*[1] can be observed until 365 K, along with a smaller increase in *t*[2]. The loadings of the first PC (*p*[1], Fig. 5B) are positively correlated to the TP anhydrate spectrum and negatively correlated to the TP monohydrate spectrum. Thus, the change in *t*[1] is associated with the solid state change from the monohydrate to the anhydrate crystal structure.

With further heating, little change can be observed in *t*[1]. However, *t*[2] sharply increases at 362 K and subsequently decreases back to its original value at 386 K, followed by a further decrease until heating is terminated at 437 K. Inspection of *p*[2] (Fig. 5B) reveals that the loadings for the second PC have a strong resemblance to the water vapour spectrum. The evaporation step of the hydrate water from the sample pellet can be clearly separated from the phase transition through *t*[1] and *t*[2].

The further decrease in *t*[2] after the water vapour signal is associated with peak broadening and red shifting in the anhydrate spectrum until the experiment is terminated.

4. Conclusions

Anhydrous and hydrated forms of crystalline pharmaceutical materials can easily be distinguished using TPS. Spectra recorded at 90 K indicate that several features at room temperature are multiple overlapping modes. It was demonstrated how variable temperature TPS can be used to monitor dehydration *in situ*. As terahertz spectra represent information on both intermolecular interactions in solid samples and rotational transitions in the gas phase it is possible to observe the phase transition during dehydration and in a second step the evaporation of the hydrate water from the sample. This makes TPS a valuable technique for the study of dehydration mechanisms.

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