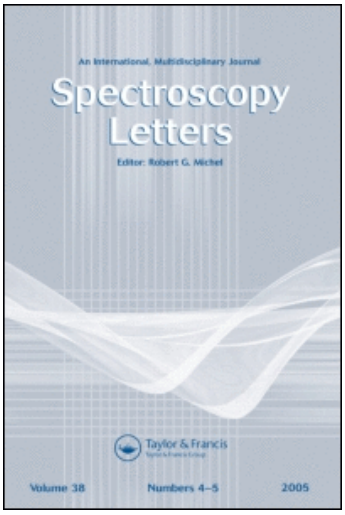

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Abstract: Time-domain terahertz (THz) spectroscopy has been used to characterize polymorphic transformations in polycrystalline theophylline, a widely used pharmaceutical compound. On transformation, different intermolecular bonding arrangements arise owing to changes in the lattice structure of the molecular crystal, leading to distinct THz spectral signatures. Temperature-dependent THz absorption measurements in anhydrous theophylline confirm that the observed vibrational modes originate from phonons within the crystal structure.

Keywords: Intermolecular forces, lattice phonons, pharmaceutical, terahertz spectroscopy, theophylline

INTRODUCTION

Active pharmaceutical products can often exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids. Each form displays unique physico-chemical properties that can profoundly influence the bioavailability, manufacturability, purification, stability, and other performance characteristics of the drug.[1] Characterization of the diversity of these solid forms is necessary to determine the form that exhibits the most appropriate balance of critical properties required in a specific drug product. It also provides a means to study molecular recognition and supramolecular assemblies formed by noncovalent interactions (hydrogen bonds, van der Waals forces, $\pi-\pi$ stacking, and electrostatic interactions) and their effect on material properties.[2]

Theophylline, an oral bronchodilator in asthma therapy, has been reported to exist in different crystal forms (polymorphism) (Fig. 1); specifically,

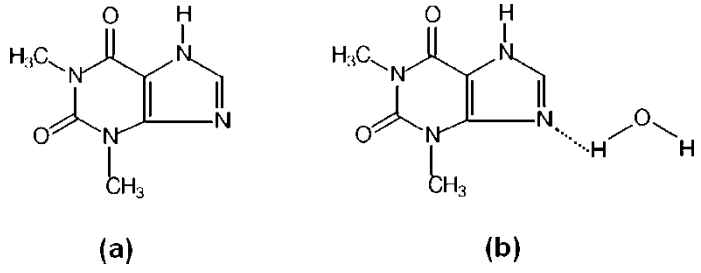

Figure 1. Chemical structures of theophylline (a) anhydrate (polymorph I and II) and (b) monohydrate.

theophylline has been shown to exist in a monohydrate form and an enantiotropic pair of anhydrous polymorphs (polymorphs I and II), where polymorph II is stable at room temperature.[3,4] Theophylline is susceptible to phase transitions between these polymorphic forms under varying crystal environments such as temperature and humidity.[4,5] As these crystal forms are known to have different physico-chemical properties that affect processing and product performance,[5] characterization of theophylline's forms, together with any intermediate phases arising during the transformations, has enormous practical relevance.

A number of different techniques have been used to characterize each of theophylline's polymorphic forms. These include powder X-ray diffraction (PXRD); optical and scanning electron microscopy in conjunction with other analytical methods; thermal analysis; nuclear magnetic resonance; and vibrational spectroscopy, including both infrared (IR) and Raman spectroscopy.[2–5] However, despite the use of these many characterization techniques, the fundamental mechanisms and molecular properties that drive crystal form diversity in theophylline, specifically the nucleation of polymorphic forms, are not in general well understood.[1] Currently, the best characterized theophylline structure is that of the monohydrate. This structure belongs to the monoclinic $P2_1/n$ space group in which an infinite chain of water molecules is attached, via hydrogen bonds, to the theophylline molecules in the (001) planes of the crystal.[6,7] In contrast, the structures of the anhydrous polymorphs (I and II) are less well known, although they have been shown to have an orthorhombic structure.[7,8] Smith et al.[9] have used theoretical and numerical approaches to study the crystal structure of anhydrous polymorphs of theophylline (the PXRD data in Ref. [9] being consistent with that obtained for polymorph II in the current work). They concluded that the crystal structure of polymorph II is formed by an N–H···N hydrogen bonding motif and proposed a detailed model of bonding within the polymorphic crystal.

Terahertz (THz) time-domain spectroscopy[10,11] has enabled the study of the structural dynamics of different crystal forms because the typical energies characterizing the intermolecular interactions fall in the far-infrared region (0.1–4.0 THz).[12,13] Indeed initial demonstrations, with application to pharmaceutical products such as ranitidine hydrochloride[14] and carbamazepine,[15] have recently been reported. Low-frequency modes of these solids primarily depend on vibrational motion around the lattice. THz spectroscopy is thus a sensitive technique to characterize such vibrational modes and a useful technique to monitor polymorphism and crystallinity of solids. In this article, the different polymorphic forms of theophylline are characterized in the frequency range 0.3–5.0 THz, using a broadband THz spectrometer. We also demonstrate the use of time-domain THz spectroscopy to characterize the gradual transformations between forms, achieved by controlled heating of the theophylline samples.

MATERIALS AND METHODS

Terahertz Spectroscopy

The THz spectroscopy system used for this work has been reported in detail elsewhere.[16] In brief, a broadband (0.3–12.0 THz) far-infrared pulse was collimated and focused onto the sample using a pair of parabolic mirrors. The transmitted THz pulse was then collected and focused using another pair of parabolic mirrors onto the surface of a photoconductive antenna for detection. The spectral resolution was $\sim$75 GHz (2.5 cm^{-1}), and purging with dry nitrogen gas was used to reduce the effects of water vapor absorption. Spectroscopic information was obtained by comparing the time-domain THz electric field recorded with, and without, a sample in the beam path. For low-temperature spectroscopic measurements, the sample was fixed onto the cold finger of a cryostat equipped with high-density polythene windows (MicrostatHe, Oxford Instruments, Oxon, UK).

Sample Preparation

Anhydrous theophylline (polymorph II) was purchased from Sigma-Aldrich Co., Dorset, UK (batch no. 093K0122). Theophylline monohydrate (also known as a pseudo-polymorph of theophylline) was prepared by recrystallization from a saturated solution of anhydrous theophylline, and polymorph I was obtained by heating polymorph II at 250°C for 5 hr. Crystalline samples prepared in this way were mixed with polytetrafluoroethylene (PTFE) powder in a mass ratio of 12:1 (PTFE:sample) and pressed into pellets (with an approximate thickness of 1 mm) for THz measurements. PTFE is transparent over a broad frequency band and an ideal matrix for far-infrared measurements up to 6.0 THz. Spectral artifacts owing to scattering from the matrix particles were effectively eliminated by the use of micrometer-sized particles (average size $\sim$1 μm), minimizing the contribution of scattering to the background absorption.

RESULTS AND DISCUSSION

Far-Infrared Signatures of Theophylline

Figure 2 shows the THz absorption spectra of polymorphs I, II and the monohydrate measured at room temperature. Each form can be distinguished by its characteristic resonance frequencies, and this categorization was confirmed by IR and PXRD measurements (not shown here) of the same samples. The differences in the observed vibrational modes between each form arise from the different local crystal environments, induced by different nearest-neighbor interactions,

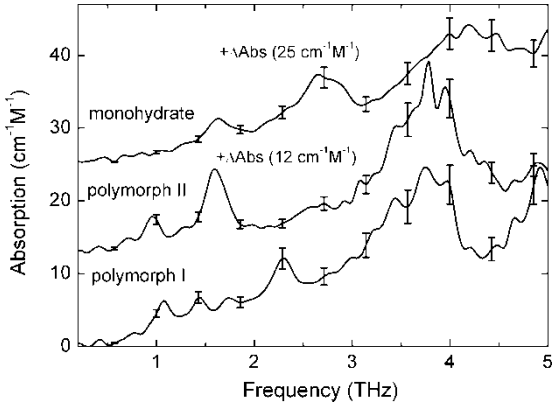

Figure 2. Comparison of the room temperature far-infrared absorption in different crystal forms of theophylline (polymorphs I and II, and the monohydrate). The spectra are vertically offset for clarity by 12 cm = 1M = 1 (polymorph II) and 25 cm = 1M = 1 (monohydrate).

as described earlier. Because the samples used in these measurements are polycrystalline, as confirmed by X-ray analysis, and there is extensive hydrogen-bonding in these crystals,[7,8] the observed modes are expected to be a result of collective intermolecular vibrations of molecules in the crystal lattice (i.e., phonons).[17–19] The intermolecular forces that define the lattice potential therefore determine the characteristic vibrational frequencies.[20]

The gradual transformations of monohydrate to polymorph II, and polymorph II to polymorph I, are shown in Fig. 3. For each data set, the samples were allowed to cool to room temperature after the heat treatment, compressed into a pellet, and measured at room temperature in the THz spectroscopy system. The time taken between heat treatment, compression into a pellet, and measurement was shown not to affect the observed spectra. For both transformations, the spectra at intermediate stages possess absorption features of both initial and final crystal forms and are also identified with characteristic refractive index changes (Fig. 3). For example, during the transformation of monohydrate to polymorph II (Fig. 3a), the intensity of the peak at 2.68 THz decreases as the temperature is increased, whereas the resonance at 1.64 THz shifts to lower frequency (1.59 THz) and the absorption intensity increases. The observed frequency shift during this transformation can be attributed to a change in the strength of the hydrogen bonded network. In addition, polymorph II displays an additional absorption peak at lower frequency (0.95 THz), not observed in the monohydrate.

Temperature-Dependent Absorption

Figures 4a and 4b show the absorption spectra and corresponding index change, respectively, of anhydrous theophylline (polymorph II) over the temperature

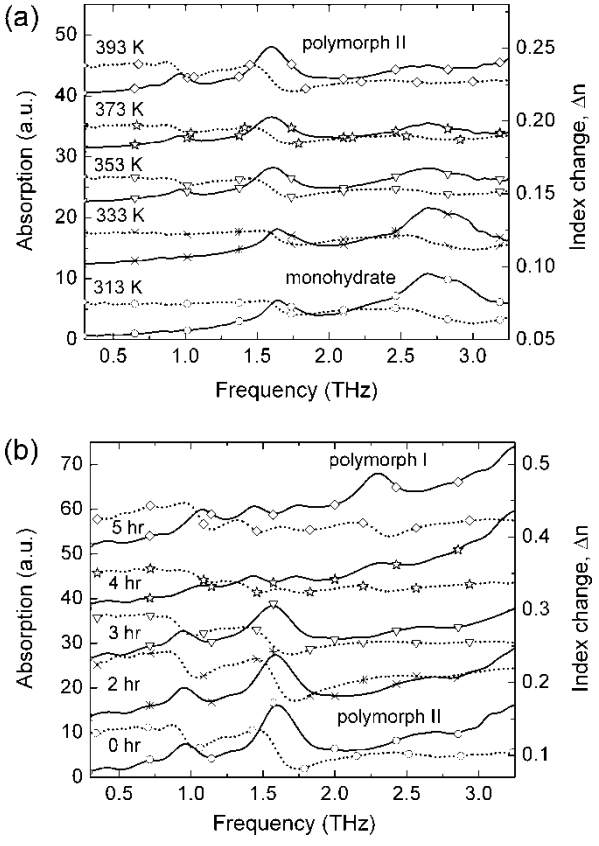

Figure 3. The room temperature absorption (solid line) and refractive index change (dotted line) during the transformation from (a) monohydrate to polymorph II by heating the monohydrate at different elevated temperatures for 5 min and (b) polymorph II to polymorph I by heating polymorph II at 523 K for different periods of time. The spectra are vertically offset for clarity. Each absorption curve and its corresponding refractive index curve are plotted with legends of the same type.

range 4–295 K. As the temperature was reduced from room temperature to 4 K, the observed absorption bands resolve into narrower peaks and shift toward higher frequencies, with different features shifting by different amounts. For example, the peak centered at 1.75 THz (at 4 K) has a stronger temperature dependence compared with other modes. Fine spectral features can be seen within this broad absorption band (FWHM ~0.24 THz at 4 K) but are not well resolved owing to the spectral resolution of our spectrometer (~75 GHz).

In earlier work,[17] the temperature-dependent frequency shift of the absorption peak [$\upsilon(T)$] was fitted to a Bose–Einstein distribution[21] on the basis that these features originate from phonons, in this case intermolecular vibrational modes mediated by hydrogen bonds in the crystal lattice.

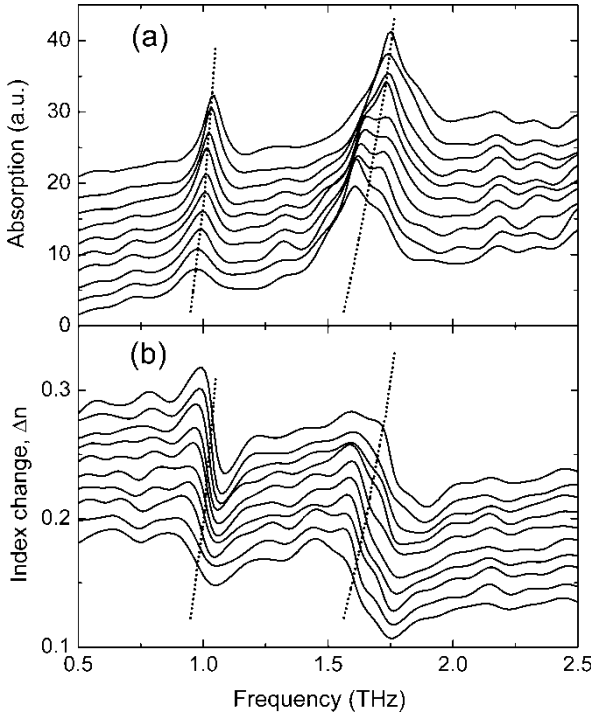

Figure 4. (a) Example THz absorption spectra and (b) the corresponding refractive index change of anhydrous theophylline (polymorph II) at 4, 45, 74, 106, 135, 166, 195, 226, 255, and 295 K (from top to bottom). The spectra are vertically offset for clarity. The shift to lower frequency with increasing temperature is clearly seen and is identified by dashed lines, which are shown as a guide to the eye.

Therefore, we expect:

$$\upsilon(T) = \upsilon_0 - \frac{AT_c}{e^{T_c/T} - 1} \tag{1}$$

where υ_0 is the center frequency of the vibration mode at 0 K and A is a constant representing the degree of dependence of the frequency shift on temperature. T_c is a characteristic temperature related to the energy of the effective phonon. In Figure 5, we show the fit to the peak centered at 1.75 THz at 4 K. (The position of the peak is identified as the frequency at which maximum amplitude occurs.) Good agreement is found over the entire temperature range, and the fitting parameters are shown in the inset. A similar behavior is observed for individual features of other theophylline polymorphs and can be explained by the anharmonicity of the vibrational potential[17]: a temperature-dependent change in the distribution of occupied energy states leads to the observed frequency shift and peak broadening/narrowing.[17,18] This supports our argument that the observed

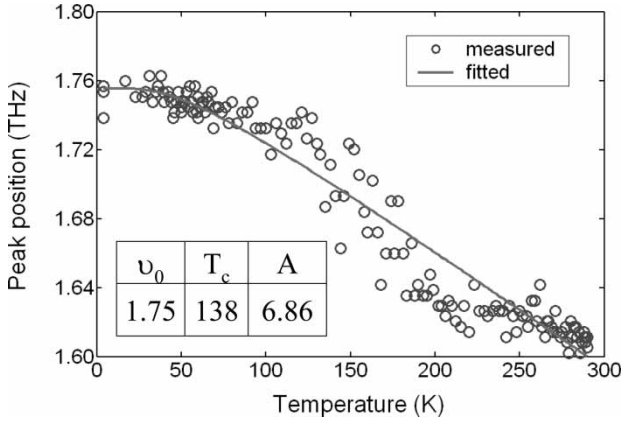

Figure 5. Temperature-dependent shift in the position of the resonance peak of anhydrous theophylline (polymorph II) centered at 1.75 THz (at 4 K). The open circles are experimental data and the solid line represents the theoretical fit. The inset shows the best-fitting parameters in units of THz, K, and 10^{-4} THz/K for υ_0, T_c and A, respectively.

vibrational modes in each of the polymorphs of theophylline have a lattice (phonon) origin, mediated by hydrogen bonds.

In summary, lattice transitions in theophylline have been characterized using time-resolved THz spectroscopy. Each polymorph is uniquely identified by a set of vibrational modes, which originate from the collective vibrations of molecules in the crystal lattice. Specific mode assignment of each of the polymorphs still, however, requires further experimental and theoretical research. Nevertheless, THz time-domain spectroscopy has a clear potential for monitoring polymorphic transitions in solids and is thus of direct relevance to the pharmaceutical industry.

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REFERENCES

1. Monissette, S. L.; Almarsson, O.; Peterson, M. L.; Remenar, J. F.; Read, M. J.; Lemmo, A. V.; Ellis, S.; Cima, M. J.; Gardner, C. R. High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids. *Adv. Drug Deliv. Rev.* **2004**, *56* (3), 275–300.

2. Rodriguez-Spong, B.; Price, C. P.; Jayasankar, A.; Matzger, A. J.; Rodriguez-Hornedo, N. General principles of pharmaceutical solid polymorphism: a supramolecular perspective. *Adv. Drug Deliv. Rev.* **2004**, *56* (3), 241–274.
3. Suzuki, E.; Shimomura, K.; Sekiguchi, K. Thermochemical study of theophylline and its hydrate. *Chem. Pharm. Bull.* **1989**, *37* (2), 493–497.
4. Suihko, E.; Ketolainen, J.; Poso, A.; Ahlgren, M.; Gynther, J.; Paronen, P. Dehydration of theophylline monohydrate—a two step process. *Int. J. Pharm.* **1997**, *158*, 47–55.
5. Suihko, E.; Lehto, V. P.; Ketolainen, J.; Laine, E.; Paronen, P. Dynamic solid-state and tableting properties of four theophylline forms. *Int. J. Pharm.* **2001**, *217* (1–2), 225–236.
6. Sun, C. Q.; Zhou, D. L.; Grant, D. J.W.; Young, V. G. Theophylline monohydrate. *Acta Crystallogr. E* **2002**, *58*, O368–O370.
7. Sutor, D. J. The structures of the pyrimidines and purines. VI. The crystal structure of theophylline. *Acta Crystallogr.* **1958**, *11*, 83–87.
8. Naqvi, A. A.; Bhattacharya, G. C. Crystal data for anhydrous theophylline. *J. Appl. Crystallogr.* **1981**, *14*, 464.
9. Smith, E. D. L.; Hammond, R. B.; Jones, M. J.; Roberts, K. J.; Mitchell, J. B. O.; Price, S. L.; Harris, R. K.; Apperley, D. C.; Cherryman, J. C.; Docherty, R. The determination of the crystal structure of anhydrous theophylline by X-ray powder diffraction with a systematic search algorithm, lattice energy calculations, and ^{13}C and ^{15}N solid-state NMR: A question of polymorphism in a given unit cell. *J. Phys. Chem. B* **2001**, *105* (24), 5818–5826.
10. Grischkowsky, D.; Keiding, S.; Van Exter, M.; Fattinger, C. Far-infrared time-domain spectroscopy with terahertz beams of dielectrics and semiconductors. *J. Opt. Soc. Am. B* **1990**, *7* (10), 2006–2015.
11. Ferguson, B.; Zhang, X. C. Materials for terahertz science and technology. *Nat. Mater.* **2002**, *1* (1), 26–33.
12. Walther, M.; Plochocka, P.; Fischer, B.; Helm, H.; Jepsen, P. U. Collective vibrational modes in biological molecules investigated by terahertz time-domain spectroscopy. *Biopolymers* **2002**, *67* (4–5), 310–313.
13. Johnston, M. B.; Herz, L. M.; Khan, A. L. T.; Kohler, A.; Davies, A. G.; Linfield, E. H. Low-energy vibrational modes in phenylene oligomers studied by THz time-domain spectroscopy. *Chem. Phys. Lett.* **2003**, *377* (1–2), 256–262.
14. Taday, P. F.; Bradley, I. V.; Arnone, D. D.; Pepper, M. Using terahertz pulse spectroscopy to study the crystalline structure of a drug: A case study of the polymorphs of ranitidine hydrochloride. *J. Pharm. Sci.* **2003**, *92* (4), 831–838.
15. Strachan, C. J.; Rades, T.; Newnham, D. A.; Gordon, K. C.; Pepper, M.; Taday, P. F. Using terahertz pulsed spectroscopy to study crystallinity of pharmaceutical materials. *Chem. Phys. Lett.* **2004**, *390* (1–3), 20–24.
16. Shen, Y. C.; Upadhya, P. C.; Beere, H. E.; Linfield, E. H.; Davies, A. G.; Gregory, I. S.; Baker, C.; Tribe, W. R.; Evans, M. J. Generation and detection of ultrabroadband terahertz radiation using photoconductive emitters and receivers. *Appl. Phys. Lett.* **2004**, *85* (2), 164–166.
17. Shen, Y. C.; Upadhya, P. C.; Davies, A. G.; Linfield, E. H. Temperature-dependent low-frequency vibrational spectra of purine and adenine. *Appl. Phys. Lett.* **2003**, *82* (14), 2350–2352.
18. Upadhya, P. C.; Shen, Y. C.; Davies, A. G.; Linfield, E. H. Far-infrared vibrational modes of polycrystalline saccharides. *Vib. Spectrosc.* **2004**, *35*, 139–143.

19. Fischer, B.; Walther, M.; Jepsen, P. U. Far-infrared vibrational modes of DNA components studied by terahertz time-domain spectroscopy. *Phys. Med. Biol.* **2002**, *47*, 3807–3814.
20. Morris, K. R.; Griesser, U. J.; Eckhardt, C. J.; Stowell, J. G. Theoretical approaches to physical transformations of active pharmaceutical ingredients during manufacturing processes. *Adv. Drug Deliv. Rev.* **2001**, *48*, 91–114.
21. Vina, L.; Logothetidis, S.; Cardona, M. Temperature-dependence of the dielectric function of germanium. *Phys. Rev. B* **1984**, *30* (4), 1979–1991.