A Novel Analytical Method for Pharmaceutical Polymorphs by Terahertz Spectroscopy and the Optimization of Crystal Form at the Discovery Stage

Yukihiro Ikeda,*[,a] Yoko Ishihara,[a] Toshiya Moriwaki,[a] Eiji Kato,[b] and Katsuhide Terada[c]

[a] *Discovery Research Center, Pharmaceutical Research Division, Takeda Pharmaceutical Company, Ltd.; 2–17–85 Jusohonmachi, Yodogawa-ku, Osaka, Osaka 532–8686, Japan:* [b] *Advantest Corporation, Ltd.; 48–2 Matsubara, Kamiayashi, Aoba-ku, Sendai, Miyagi 989–3124, Japan: and* [c] *School of Pharmaceutical Sciences, Toho University; 2–2–1 Miyama, Funabashi, Chiba 274–8540, Japan.*

Received September 8, 2009; accepted October 26, 2009; published online October 29, 2009

A novel analytical method for the determination of pharmaceutical polymorphs was developed using terahertz spectroscopy. It was found out that each polymorph of a substance showed a specific terahertz absorption spectrum. In particular, analysis of the second derivative spectrum was enormously beneficial in the discrimination of closely related polymorphs that were difficult to discern by powder X-ray diffractometry. Crystal forms that were obtained by crystallization from various solvents and stored under various conditions were specifically characterized by the second derivative of each terahertz spectrum. Fractional polymorphic transformation for substances stored under stressed conditions was also identified by terahertz spectroscopy during solid-state stability test, but could not be detected by powder X-ray diffractometry. Since polymorphs could be characterized clearly by terahertz spectroscopy, further physicochemical studies could be conducted in a timely manner. The development form of compound examined was determined by the results of comprehensive physicochemical studies that included thermodynamic relationships, as well as chemical and physicochemical stability. In conclusion, terahertz spectroscopy, which has unique power in the elucidation of molecular interaction within a crystal lattice, can play more important role in physicochemical research. Terahertz spectroscopy has a great potential as a tool for polymorphic determination, particularly since the second derivative of the terahertz spectrum possesses high sensitivity for pharmaceutical polymorphs.

Key words polymorph; terahertz spectroscopy; second derivative; thermodynamic solubility; stable form

Crystal polymorphs are defined as substances that are chemically identical but exist in more than one crystal form, and generally differ in physicochemical properties. The polymorphism is a common phenomenon among pharmaceuticals. It has been shown that about 80% of active pharmaceutical ingredients (API) have polymorphs.[1,2]

The optimization of polymorphic forms of an API is an important area of physicochemical research in drug discovery. The impact of polymorphs has been widely reported in the literatures, affecting such properties as dissolution rates, solubility, bioavailability and manufacturability.[3—7]

The detection of polymorphs in drug discovery and manufacturing process is very important for assuring sufficient quality of the API. Powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC), IR spectroscopy, Raman spectroscopy and solid state NMR measurement are generally applied for polymorph analysis of APIs. Although most of polymorphs are identifiable by these analytical techniques, there are some difficult cases to identify.

In a previous paper,[8] we reported on remarkably similar polymorphs, forms A and B of Compound A, which is a novel drug for the treatment of osteoporosis. They were discriminated only by high-resolution powder X-ray diffractometry and thermally stimulated current (TSC) measurements. In particular, the TSC technique was useful for the discrimination of Compound A polymorphs, since both forms gave completely different TSC patterns.

The terahertz (THz) region of the electromagnetic spectrum lies between the infrared and millimeter wave regions around 0.3 to 10 THz. THz spectroscopic analysis has been proposed as an analytical technique for crystal polymorphs because of the typical energies characterizing intermolecular interactions in a crystal lattice correspond to the THz region.[9] The assignment of spectral features in this regime is still subject to scientific debate and several experiments have been discussed.[10—12] Crystalline APIs also have unique phonon modes, and as such, polymorphic forms of solid formulations have different THz spectra.[13—16] In addition, the absence of distinct modes in amorphous or liquid crystalline forms has been demonstrated.[17—19] Thus, THz spectroscopy is thought to be an effective tool for readily discriminating polymorph, even when their crystalline structures are quite similar.

In this paper, we demonstrate THz spectroscopy as a novel analytical procedure for the determination of pharmaceutical polymorphs. We have shown that polymorphs of tolbutamide, carbamazepine and Compound A show slight different THz absorption spectra from each other and the second derivative of the THz absorption spectrum is an enormously beneficial tool for discerning different polymorphs.

After the polymorph characterization, the optimization of the crystal form is an important step in the development of an API. To avoid the polymorph trouble during manufacturing and storage such as in the Ritonavir nightmare,[20,21] from the viewpoint of drug development it is preferable to identify the stable form from the start. It is important to resolve the thermodynamic relationship between polymorphs of a compound to decide the development form. The thermodynamic relationship between the Compound A polymorphs was clarified by the measurements of thermodynamic solubility of both forms. Furthermore, chemical and physicochemical stability of both forms were investigated. The development form of Compound A was determined by these comprehensive physicochemical studies.

* To whom correspondence should be addressed. e-mail: Ikeda_Yukihiro@takeda.co.jp

Experimental

Materials Tolbutamide polymorphs, forms I and III were prepared by crystallzation from dichloromethane-heptane and ethanol, respectively.[22] Form II was obtained from suspension in ethanol at 40 °C. Carbamazepine was obtained from Wako Pure Chemical Industry, Ltd. The commercial product was supplied as form III. Form I was prepared by heating form III at 170 °C for 2 h, as described by McMahon *et al.*[23] Form II was prepared by recrystallization of form III from cyclohexane.[24] The crystal form of each materials was confirmed by PXRD.

Compound A was synthesized in the Medicinal Chemistry Research Laboratories and the Chemical Development Laboratories at Takeda Pharmaceutical Co., Ltd. Form A was obtained by the crystallization from 2-propanol solution saturated with Compound A at 50 °C and then stirring at room temperature. Form B was prepared by dissolving excess Compound A in ethanol at 50 °C and then stirring overnight at room temperature.

Special grade or HPLC grade reagents were obtained from Wako Pure Chemical Industry, Ltd.

Powder X-Ray Diffractometry About 4 mg of sample was loaded into a non-reflective holder made of single crystal silicon. The X-ray source was Cu$K\alpha$ (λ=1.5418 Å) and the diffraction beam was monochromated by a bent-graphite monochromator. Other conditions were as follows: voltage, 40 kV; current, 50 mA; scatter and receiving slits, 0.45 mm; scanning speed, 6°/min; diffraction angle (2θ), 3 to 40° (RINT 2100 diffractometer, Rigaku Co., Ltd., Tokyo, Japan). The crystallinity of each sample was calculated by Hermans method.[25,26]

Terahertz Spectroscopy. Sample Preparation Powder of polymorphic forms A and B of Compound A was gently ground using a pestle and mortar to reduce the particle size respectively. Then mixing the each sample with polyethylene (PE) powder (mean particle size 7 to 9 μm) using a pestle and mortar for geometric dilution. The concentration of forms A and B was 5% w/w in PE powder. PE powder is conventionally used as a binder and diluent for THz spectroscopy. PE powder was selected because it exhibits very low frequency absorption in the THz regime, thus allowing the spectra of compound A to be measured in the absence of background signal from other materials. Circular discs of sample tablets of mass 105 mg and 10 mm diameter were prepared using a hydraulic press (model P-16B, Riken Seiki Co., Niigata, Japan) with 7 MPa compression for 10 min after 5 min preparatory evacuation using rotary pump model (G25-SA, Ulvac Kiko Inc., Kanagawa, Japan). All samples were prepared in triplicate. A 100% w/w PE tablet (100 mg) was also prepared for background determination.

Terahertz Measurement Transmission THz spectra were obtained using the specialized Fourier transform spectrometer for terahertz spectral measurement set up by Advantest Corporation, Ltd. (Tokyo, Japan). Figure 1 shows a schematic diagram of the spectrometer. The light source was equipped with a high voltage mercury lamp and a Michelson interferometer with silicon beam splitter. The signal passed through the sample was detected by helium-cooled (4.2 K) silicon bolometer (Infrared Laboratories, AZ, U.S.A.). During the measurement, the sample chamber was held under vacuum (approximately 2500 Pa) to eliminate the absorption of water vapor.[27] Samples were measured over the frequency range 0.5 to 10 THz at a resolution of 60 GHz. THz spectra thus obtained were the average of 32 scans (approximately 1-min measuring time).

Crystallization from Various Solvents About 20 mg of form B was dissolved in appropriate volumes of methanol, ethanol, 2-propanol, acetonitrile, acetone, isopropyl ether and ethyl acetate at 50 °C to give a saturated solution. The solution was then filtered through a membrane filter (pore size: 0.2 μm). The filtrate was cooled to 5 °C with stirring overnight. The crystals thus obtained were isolated by decantation and dried under nitrogen gas stream.

Four volumes of water or heptane were added to ethanol or 2-propanol saturated solutions to give crystals from these solvents. Crystals were prepared and isolated as described above.

Stability in the Solid State About 5 mg of forms A and B of Compound A was weighed accurately into a colorless glass bottle. Bottles were either sealed with a screw cap and at 80 °C, or left open and stored at 60 °C/75% RH (oven model LH21-15M, Nagano Science Co., Ltd., Osaka, Japan).

After storage, each sample was dissolved in a mixture of acetonitrile and 50 mmol/l ammonium acetate (1 : 1) and transferred to a 25 ml volumetric flask. The sample solution was prepared to make exactly 25 ml with a mixture of acetonitrile and 50 mmol/l aqueous ammonium acetate solution (1 : 1). The sample solution and the standard solution prepared with a frozen stored sample were analyzed by HPLC (model 2795, Waters Co., Ltd., U.S.A.).

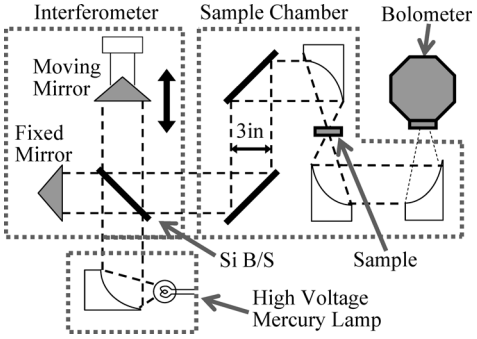

Fig. 1. Schematic of THz Fourier Transform Spectrometer

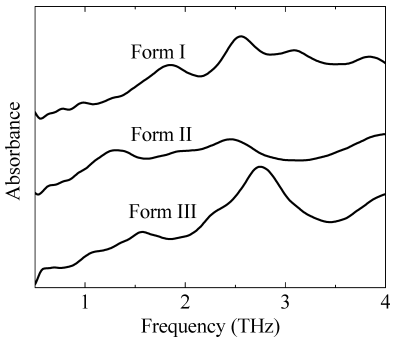

Fig. 2. THz Absorption Spectra of Tolbutamide Polymorphs

Analytical conditions were as follows: detection, UV 270 nm; column, YMC ProC18 150 mm length and 4.6 mm diameter; mobile phase A, 50 mmol/l aqueous ammonium acetate; mobile phase B, acetonitrile; gradient program, mobile phase B 35% for 0 to 10 min, B from 35 to 80% for 10 to 20 min, B 80% for 20 to 30 min; column temperature, constant temperature about 40 °C; flow rate, 1.0 ml/min; and injection volume, 20 μl.

Crystalline stability of the stored samples was tested by PXRD and THz spectroscopy as described above.

Thermodynamic Solubility About 2 mg of each compound was weighed into a glass tube. About 2 ml of Britton–Robinson buffer solution (pH 3.0) was added to each tube and incubated at 20 °C, 30 °C, 37 °C and 50 °C with shaking at 100 rpm for 2 h (BioShaker M-BR-022, Taitec Co., Saitama, Japan). After incubation, the saturated solution was filtered with a membrane filter (pore size: 0.2 μm). The filtrate was diluted adding the same volume of a mixture of acetonitrile and 10 mmol/l phosphate buffer solution (pH 3.0) (1 : 1) and analyzed by HPLC.

Results and Discussion

Polymorphic Characterization of Tolbutamide and Carbamazepine by Terahertz Spectroscopy Tolbutamide and carbamazepine were used as model compounds to demonstrate polymorphic characterization by THz spectroscopy, since polymorphic properties of these polymorphs have been closely examined in several different studies.[14,22,28—30]

The THz transmission spectra of tolbutamide polymorphs were obtained and converted to the absorption spectra. The absorption spectra are shown in Fig. 2. The spectrum of each sample was the average of three independent samples that were smoothed using the Savitzky–Golay algorithm (second order polynomials fitted with 13 points) to remove noise or etaloning artifacts. Comparison of the spectra for forms I, II and III of tolbutamide showed subtle differences between each other.

The second derivative of the THz spectrum was examined

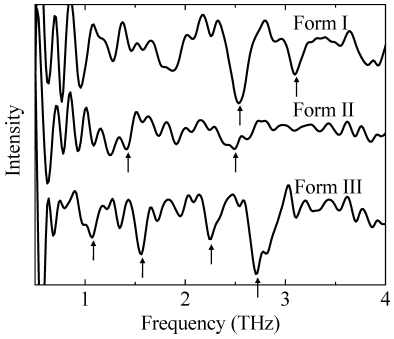

Fig. 3. Second Derivative of the THz Absorption Spectra for Tolbutamide Polymorphs

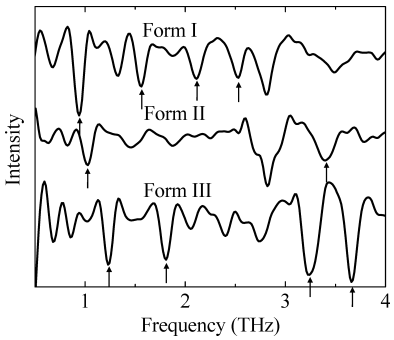

Fig. 4. Second Derivative of the THz Absorption Spectra for Carbamazepine Polymorphs

to distinguish the polymorphs clearly. Figure 3 shows the Savitzky–Golay second derivative of each THz spectrum for the tolbutamide polymorphs. In Fig. 3, the spectral peaks of the tolbutamide polymorphs, indicated by arrows, were more distinguishable than in Fig. 2. The characteristic peaks of tolbutamide form I were found at 2.5 and 3.1 THz. Those of form II were detected at 1.4 and 2.4 THz, while those of form III were found at 1.1, 1.6, 2.2 and 2.7 THz.

In carbamazepine, spectral differences between polymorphs also became clear by second derivative analysis. Carbamazepine form I showed characteristic peaks at 0.9, 1.3, 2.1 and 2.5 THz. Characteristic peaks of form II were detected at 1.0 and 3.4 THz, although both peaks had weak intensity. In contrast, those of forms III were found 1.2, 1.8, 3.2 and 3.7 THz clearly. The characteristic peaks of each form are indicated by arrows in Fig. 4. The peaks of forms I and III in less than 2.5 THz region agree well with the reported values.[17] Additionally, some novel characteristic peaks were found in more than 2.5 THz region.

Tolbutamide and carbamazepine polymorphs were characterized by THz spectroscopy and its second derivative. It was clarified that THz spectroscopy is applicable to polymorphic characterization and the second derivative of the THz spectrum is particularly useful in analyzing pharmaceutical polymorphs.

Polymorphic Characterization of Compound A by Terahertz Spectroscopy PXRD patterns of Compound A forms A and B are shown in Fig. 5. They showed remarkably similar diffraction peaks, making it difficult to distinguish A from B by PXRD. The crystallinity of forms A and B determined by Hermans method was 66% and 83%, respectively. Both

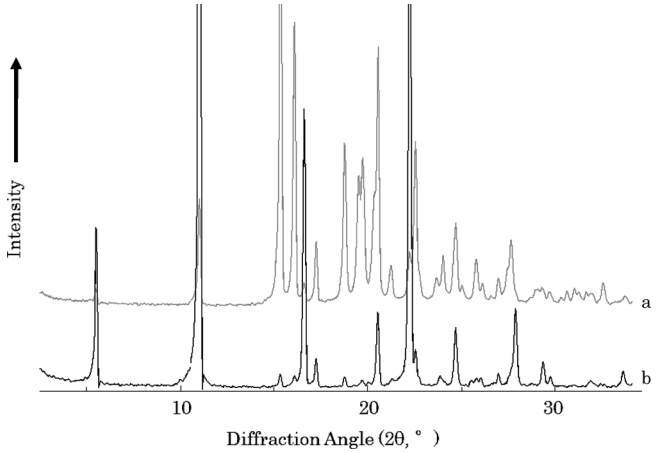

Fig. 5. Powder X-Ray Diffraction Patterns of Compound A Polymorphs
a) Form A, b) form B.

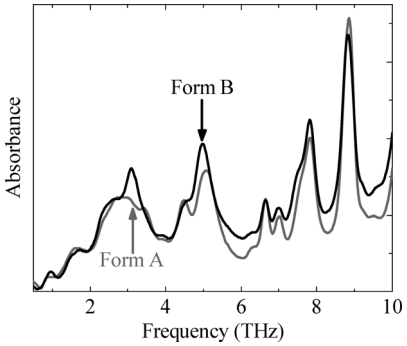

Fig. 6. THz Absorption Spectra of Compound A Polymorphs

forms showed sufficient crystallinity to qualify as an API.

Figure 6 shows the absorption spectra for polymorphs A and B of Compound A. Comparison of the spectra for forms A and B shows some differences in peaks between polymorphs, although the differences are not great. The spectrum of form B exhibited prominent peaks at 3.1 and 5.0 THz and a smaller peak at 0.9 THz, while form A exhibited peaks at 4.5 and 5.1 THz. The second derivative of the THz spectrum was calculated for forms A and B. Figure 7 shows the second derivative of each spectrum from Fig. 6. The characteristic peaks of form B were found at 0.9, 1.5, 1.8, 3.1 and 5.0 THz, while those of form A were found at 0.8, 1.6, 3.5 and 5.1 THz. The characteristic peaks of each form are indicated by arrows in Fig. 7. Since the PXRD patterns are similar, the crystal lattices of both forms appear to be almost the same. Since THz spectroscopy possesses unique power to elucidate molecular interactions within a crystal lattice, THz spectroscopy and its second derivative have great potential as an analytical tool for pharmaceutical polymorphs.

The characterization of crystal forms crystallized from various solvents was demonstrated by THz spectroscopy. None of the materials contained any volatiles, as determined by thermogravimetry. THz spectra and second derivative spectra are shown in Figs. 8 and 9. Materials crystallized from ethanol–water, 2-propanol, 2-propanol–water and isopropyl ether showed spectra matching form A, particularly the characteristic peaks of form A at 3.5 and 5.1 THz were detected (Fig. 9). Materials crystallized from ethanol,

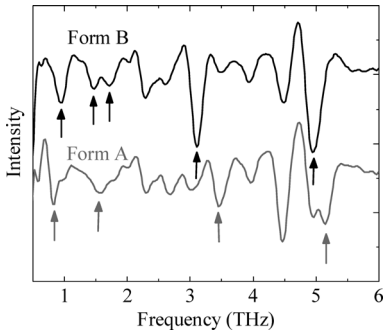

Fig. 7. Second Derivative of the THz Absorption Spectra for Compound A Polymorphs

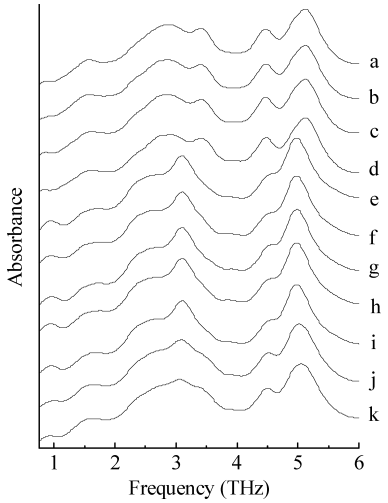

Fig. 8. THz Absorption Spectra of Compound A Crystallized from Various Solvents

a) Ethanol–water, b) 2-propanol, c) 2-propanol–water, d) isopropyl ether, e) ethanol, f) ethanol–heptane, g) 2-propanol–heptane, h) acetonitrile, i) methanol, j) acetone, k) ethyl acetate.

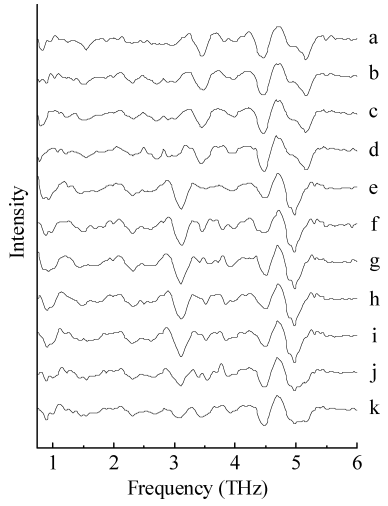

Fig. 9. Second Derivative of THz Spectra of Compound A Crystallized from Various Solvents

a) Ethanol–water, b) 2-propanol, c) 2-propanol–water, d) isopropyl ether, e) ethanol, f) ethanol–heptane, g) 2-propanol–heptane, h) acetonitrile, i) methanol, j) acetone, k) ethyl acetate.

Table 1. Stability Test Results of Compound A Polymorphs in the Solid State

	Storage condition	Period	Appearance	Purity (%)
Form A	Initial		White powder	100.0
	80 °C (closed)	1 week	White powder	99.9
		2 weeks	White powder	99.9
	60 °C/75% RH (open)	1 week	White powder	99.8
		2 weeks	White powder	99.6
Form B	Initial		White powder	100.0
	80 °C (closed)	1 week	White powder	99.9
		2 weeks	White powder	100.0
	60 °C/75% RH (open)	1 week	White powder	100.0
		2 weeks	White powder	99.9

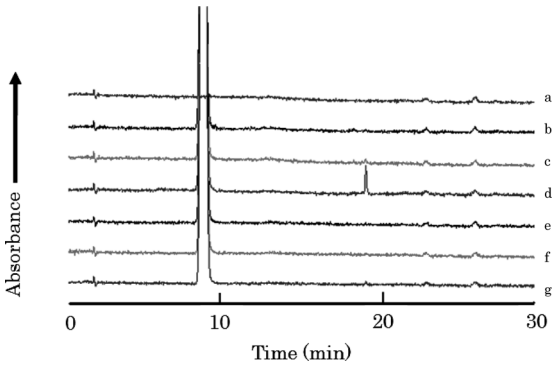

Fig. 10. HPLC Chromatograms of Polymorphs of Compound A Stored at 80 °C and 60 °C/75% RH for 2 Weeks

a) Blank (mobile phase), b) form A initial, c) form A 80 °C 2 weeks, d) form A 60 °C/75% RH 2 weeks, e) form B initial, f) form B 80 °C 2 weeks, g) form B 60 °C/75% RH 2 weeks.

ethanol–heptane, 2-propanol–heptane, acetonitrile and methanol showed the spectra matching form B, particularly based on the characteristic peaks of form B at 0.9, 3.1 and 5.0 THz. Materials crystallized from ethyl acetate and acetone showed ambivalent spectra, somewhere in between forms A and B. It was presumed that both samples were mixed crystals of forms A and B. Thus, crystal forms of various samples were discerned with clarity by THz spectroscopy and its second derivative.

Stability of Polymorphs of Compound A Chemical and physicochemical stability of Compound A forms A and B was studied. The analytical results of the chemical stability test are shown in Table 1. Form B was stable at 80 °C and 60 °C/75% RH for 2 weeks, while form A was decomposed slightly at 60 °C/75% RH. A lipophilic degradation product was detected in the HPLC chromatogram of form A stored at 60 °C/75% RH, but not for form B (Fig. 10).

The crystalline form of stored samples was analyzed by PXRD, THz spectroscopy and its second derivative. Results are shown in Figs. 11, 12 and 13, respectively. No significant change was observed in form B. On the other hand, THz spectra and the second derivative spectra of form A showed a mixture of forms A and B, although significant change was not observed by PXRD. To determine the exact difference between stored sample and initial sample, subtracted spectra of the second derivative THz absorption spectra were calculated. The results are shown in Fig. 14. Large differences were found in form A depending on storage conditions,

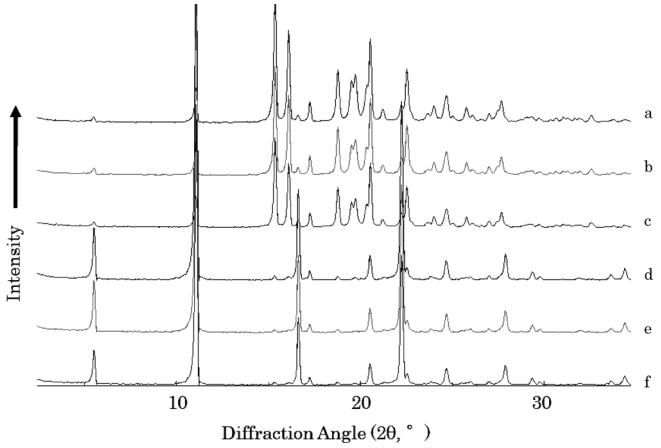

Fig. 11. PXRD Patterns of Compound A Polymorphs Stored at 80 °C and 60 °C/75% RH for 2 Weeks

a) Form A initial, b) form A 80 °C 2 weeks, c) form A 60 °C/75% RH 2 weeks, d) form B initial, e) form B 80 °C 2 weeks, f) form B 60 °C /75% RH 2 weeks.

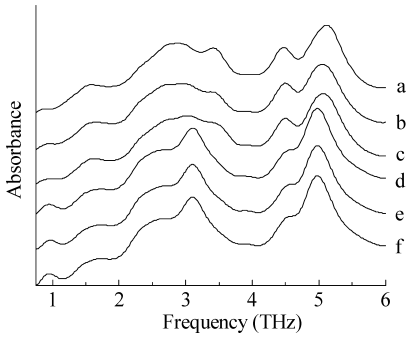

Fig. 12. THz Absorption Spectra of Compound A Polymorphs Stored at 80 °C and 60 °C/75% RH for 2 Weeks

a) Form A initial, b) form A 80 °C 2 weeks, c) form A 60 °C/75% RH 2 weeks, d) form B initial, e) form B 80 °C 2 weeks, f) form B 60 °C/75% RH 2 weeks.

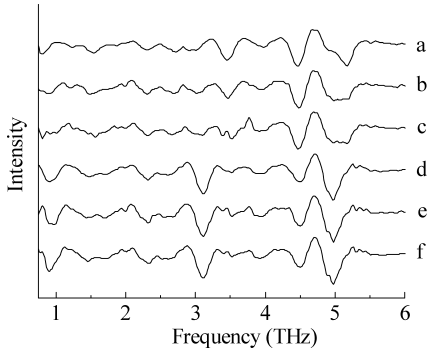

Fig. 13. Second Derivative of THz Spectra for Compound A Polymorphs Stored at 80 °C and 60 °C/75% RH for 2 Weeks

a) Form A initial, b) form A 80 °C 2 weeks, c) form A 60 °C/75% RH 2 weeks, d) form B initial, e) form B 80 °C 2 weeks, f) form B 60 °C/75% RH 2 weeks.

while little difference was found in form B.

These results indicate that form A is gradually transformed to form B during storage at 80 °C and 60 °C/75% RH. It was confirmed that THz spectroscopy is one of the more highly sensitive analytical methods for the determination of pharmaceutical polymorphs.

Thermodynamic Relationships between Polymorphs of Compound A It was not possible to determine the thermodynamically stable form by the examination of DSC parameters,[31,32] since form A of Compound A transformed to form B without any thermal events.[8] The thermodynamic solubility was measured to determine the thermodynamic relationship between forms A and B. The thermodynamic solubility of both forms in Britton–Robinson buffer solution (pH 3.0) at 20 °C, 30 °C, 37 °C and 50 °C is shown in Table 2. The van't Hoff type plots of these results are shown in Fig. 15.

Both forms showed good linearity and almost identical slope. It was determined that form B is the thermodynamically stable form around ambient temperature, because the solubility of form B was consistently lower than that of form A.

It was clarified that form B was preferable to form A as the development form, because form B was chemically stable and the thermodynamically stable form.

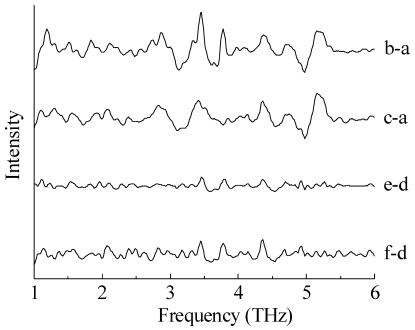

Fig. 14. Subtracted Second Derivative THz Absorption Spectra Showing Difference between Stored Sample and Initial Sample

a) Form A initial, b) form A 80 °C 2 weeks, c) form A 60 °C/75% RH 2 weeks, d) form B initial, e) form B 80 °C 2 weeks, f) form B 60 °C/75% RH 2 weeks.

Table 2. Thermodynamic Solubility of Compound A Polymorphs in Britton–Robinson Buffer Solution (pH 3.0) at Various Temperatures

Temperature	Solubility (μg/ml)	
	Form A	Form B
20 °C	28.5	22.5
30 °C	39.2	32.2
37 °C	53.9	45.4
50 °C	75.2	60.3

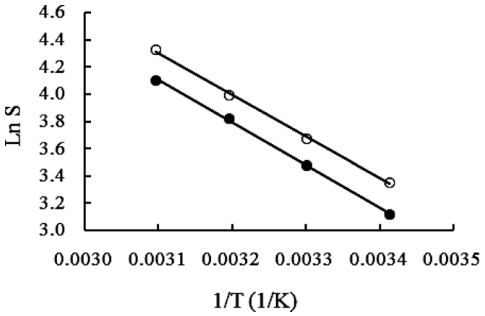

Fig. 15. Van't Hoff Type Plots of Thermodynamic Solubility of Compound A Polymorphs

○: form A, ●: form B.

Conclusion

A novel analytical method for the determination of pharmaceutical polymorphs was established by THz spectroscopy and its second derivative spectrum, and polymorphs of tolbutamide, carbamazepine and Compound A were clearly characterized. The second derivative of THz spectrum, in particular, made a significant contribution to the characterization of complicated pharmaceutical polymorphs.

Since the polymorphs of Compound A were characterized clearly by THz spectroscopy, further physicochemical studies could be completed in a timely manner. The better development form of Compound A was determined to be form B by the results of comprehensive physicochemical studies including thermodynamic analysis, as well as chemical and physicochemical stability.

In conclusion, THz spectroscopy has unique power in the elucidation of molecular interactions within a crystal lattice and can play a more important role in physicochemical research. THz spectroscopy has great potential as a general tool for polymorphic determination, with the second derivative of the THz spectrum possessing high sensitivity for pharmaceutical polymorphs.

Acknowledgement The authors are grateful to Mr. Motoki Imamura, Advantest Corporation, Ltd., for thorough analysis, technical assistance and helpful discussion. The authors would like to acknowledge Dr. Hiroyuki Kimura and members of Physicochemistry and DMPK Sciences at the Discovery Research Center of Takeda Pharmaceutical Company, Ltd. for their insight and support. We also thank Dr. Douglas Cary of the Medicinal Chemistry Laboratories of Takeda Pharmaceutical Company, Ltd. for proofreading the manuscript.

References

1) Grunenberg A., Henk J.-O., Siesler H. W., *Int. J. Pharm.*, **129**, 147—158 (1996).
2) Ikeda Y., *Farumashia*, **39**, 209—213 (2003).
3) Bryn S., Pfeiffer R., Ganey M., Hoiberg C., Poochikian G., *Pharm. Res.*, **12**, 945—954 (1995).
4) Chang L. C., Caira M. R., Guillory J. K., *J. Pharm. Sci.*, **84**, 1169—1179 (1995).
5) Gandhi R. B., Bogardus J. B., Bugay D. E., Perrone R. K., Kaplan M. A., *Int. J. Pharm.*, **201**, 221—237 (2000).
6) Khankari R., Chen L., Grant D. J. W., *J. Pharm. Sci.*, **87**, 1052—1061 (1998).
7) Bauer J., Spanton S., Henry R., Quick J., Dziki W., Porter W., Morris J., *Pharm. Res.*, **18**, 859—866 (2001).
8) Ikeda Y., Hirayama T., Terada K., *Thermochim. Acta*, **431**, 195—199 (2005).
9) Godlewska M., Ściesiński J., Ściesińska E., *Phys. Status Solidi A*, **55**, 723—734 (1979).
10) Chen Y., Liu H., Deng Y., Schauki D., Fitch M. J., Osiander R., Dodson C., Spicer J. B., Shur M., Zhang X.-C., *Chem. Phys. Lett.*, **400**, 357—361 (2004).
11) Saito S., Inerbaev T. M., Mizuseki H., Igarashi N., Kawazoe Y., *Jpn. J. Appl. Phys.*, **45**, 4170—4175 (2006).
12) Jepsen P. U., Clark S. J., *Chem. Phys. Lett.*, **42**, 275—280 (2007).
13) Taday P. F., Bradley I. V., Arnone D. D., Pepper M., *J. Pharm. Sci.*, **92**, 831—838 (2003).
14) Zeitler J. A., Newnham D. A., Taday P. F., Strachan C. J., Pepper M., Gordon K. C., Rades T., *Thermochim. Acta*, **436**, 71—77 (2005).
15) Upadhya P. C., Nguyen K. L., Shen Y. C., Obradovic J., Fukushige K., Griffiths R., Gladden L. F., Davies A. G., Linfield E. H., *Spectrosc. Lett.*, **39**, 215—224 (2006).
16) Zeitler J. A., Newnham D. A., Taday P. F., Threlfall T. L., Lancaster R. W., Berg R. W., Strachan C. J., Pepper M., Gordon K. C., Rades T., *J. Pharm. Sci.*, **95**, 2486—2498 (2006).
17) Strachan C. J., Rades T., Newnham D. A., Gordon K. C., Pepper M., Taday P. F., *Chem. Phys. Lett.*, **390**, 20—24 (2004).
18) Strachan C. J., Taday P. F., Newnham D. A., Gordon K. C., Zeitler J. A., Pepper M., Rades T., *J. Pharm. Sci.*, **94**, 837—846 (2005).
19) Zeitler J. A., Taday P. F., Pepper M., Rades T., *J. Pharm. Sci.*, **96**, 2703—2709 (2007).
20) Chemburkar S. R., Bauer J., Deming K., Spiwek H., Patel K., Morris J., Henry R., Spanton S., Dziki W., Porter W., Quick J., Bauer P., Donaubauer J., Narayanan B. A., Soldani M., Riley D., McFarland K., *Org. Process Res. Dev.*, **4**, 413—417 (2000).
21) Bauer J., Spanton S., Henry R., Quick J., Dziki W., Porter W., Morris J., *Pharm. Res.*, **18**, 859—866 (2001).
22) Hasegawa G., Komasaka T., Bando R., Yoshihashi Y., Yonemochi E., Fujii K., Uekusa H., Terada K., *Int. J. Pharm.*, **369**, 12—18 (2009).
23) McMahon L. E., Timmins P., Williams A. C., York P., *J. Pharm. Sci.*, **85**, 1064—1069 (1996).
24) Zerrouk N., Chemtob C., Arnaud P., Toscani S., Dugue J., *Int. J. Pharm.*, **225**, 49—62 (2001).
25) Hermans H. P., Weidinger A. W., *J. Appl. Phys.*, **19**, 491—506 (1948).
26) Ikeda Y., Ban J., Ishikawa T., Hashiguchi S., Urayama S., Horibe H., *Chem. Pharm. Bull.*, **56**, 1406—1411 (2008).
27) Exter M. V., Fattinger C., Grischkowsky D., *Opt. Lett.*, **14**, 1128—1130 (1989).
28) Rowe E. L., Anderson B. D., *J. Pharm. Sci.*, **73**, 1673—1675 (1984).
29) Kaneniwa N., Yamaguchi T., Watari N., Otsuka M., *Yakugaku Zasshi*, **104**, 184—190 (1984).
30) Kobayashi Y., Ito S., Itai S., Yamamoto K., *Int. J. Pharm.*, **193**, 137—146 (2000).
31) Venkatesh G. M., Barnett M. E., Owusu-Fordjour C., Galop M., *Pharm. Res.*, **18**, 98—103 (2001).
32) Yu L., *J. Pharm. Sci.*, **84**, 966—974 (1995).