Broadband terahertz time-domain spectroscopy: crystalline and glassy drug materials

Seiji Kojima, Tomohiko Shibata, Hikaru Igawa, and Tatsuya Mori
Division of Materials Science, University of Tsukuba, Tsukuba, Ibaraki 305-8573, Japan
E-mail: kojima@ims.tsukuba.ac.jp

Abstract. Low-energy IR active modes of glassy and crystalline drug materials were studied by the broadband Terahertz Time Domain Spectroscopy (THz-TDS) in the frequency range from 0.5 to 6.5 THz using a Cherenkov type THz generator. In order to determine the real and imaginary parts of complex dielectric constant, all samples were measured by the transmission using a pure pellet without mixing polyethylene. For glassy indomethacine, the broadband THz spectrum of real part of dielectric constant shows step-wise decrease with the increase of frequency, while the imaginary part shows a broad peak at about 3 THz reflecting quenched glassy disordered structure. The observed spectra of crystalline racemic ketoprofen show the noncoincidence of peak frequencies between low-frequency Raman scattering and THz absorbance spectra. It can be attributed to the fact that the mutual exclusion principle between Raman and IR activities holds below 6 THz.

1. Introduction

Vibrational spectroscopy is a powerful tool to elucidate not only the static crystal or molecular structure but also the dynamical properties related to bond strength and molecular interaction, etc. The far-IR spectroscopy has been extensively applied to various kinds of crystalline and glassy materials to investigate low-energy excitations such as ferroelectric soft modes, polaritons, excitons, boson peaks, etc., while most far-IR studies reported results on the frequency-dependent absorbance or transmittance, and the real and imaginary parts of dielectric constants were not reported.

The new technique of the coherent terahertz generation using a femtosecond pulse laser enables the unique determination of a complex dielectric constant without the Kramers-Kronig transformation, and terahertz time domain spectroscopy (THz-TDS) has attracted much attention. However, the most of the THz-TDS works until now was done below 2 THz, which is equivalent to 67 cm$^{-1}$ [1]. Very recently widely tunable monochromatic Cherenkov phase-matched THz wave generator was developed using nonlinear optic crystals of ferroelectric MgO doped LiNbO$_3$ [2]. The frequency range of THz-TDS has been extended up to 6.5 THz by such a broadband THz generator. In addition, the progress of the rapid scan method enables to acquire high quality THz spectra by the use of high-speed asynchronous optical sampling (AOS) technique [3].

In this work, transmission broadband THz spectra in the frequency range from 0.5 to 6.5 THz were studied in glassy and crystalline states of polymorphic and polymorphic drug materials by using a THz-TDS equipment with a Cherenkov type THz generator and the high-speed AOS technique. The
THz spectrum was compared with the low-frequency Raman spectrum to discuss the exclusion principle of selection rules between IR and Raman scattering spectroscopy.

2. Experimental
Indomethacin with the purity $\geq 99\%$ and racemic ketoprofen with the purity $\geq 98\%$ were purchased from Sigma-Aldrich. The glassy state of indomethacin was obtained without further purification by melt-quenching at 80 K. All spectra were measured using a thin plate or a pressed pure pellet without mixing other solid powders such as polyethylene to determine real and imaginary part of dielectric constant accurately.

THz transmission spectra were measured in the frequency range from 0.5 to 6.5 THz using a THz-TDS equipment (TAS7500SU, Advantest Co.) with a Cherenkov type THz generator and the high-speed AOS technique. The low-frequency Raman scattering spectra were measured by a single frequency green-YAG laser with wavelength 532 nm and a triple-grating monochromator (T64000, Horiba-Jobin-Yvon) with additive dispersion [4]. The comparison of THz radiation power between a conventional low-temperature grown GaAs dipole photoconductive antenna and a Cherenkov type THz generator is shown in figure 1. The photoconductive antenna has a broad peak at about 0.7 THz, while the peak frequency of a Cherenkov type is around 2.5 THz and very broad. Therefore, the latter type generator enables us to observe a broadband spectrum from 0.2 to 6.5 THz.

![Figure 1. Comparison of THz power spectra between a Cherenkov type THz generator and a dipole photoconductive antenna.](image)

3. Results and discussion
The most of drug materials are polymorphic and polyamorphic originated from multi-basin structure in the potential energy landscape. The energy of these basins is nearly degenerate, and the transition among basins can be easily occurred by the change of temperature, pressure, and other chemical conditions. The dynamical properties in the THz frequency range are very sensitive for the difference among polymorphic and polyamorphic states. Therefore, the investigation on each state is very important to give new insights into polymorphic and polyamorphic nature.

3.1. Complex dielectric constant of glassy indomethacin
The indomethacin, 1-[19]-5-methoxy-2-methylindole-3-acetic acid with chemical formula $\text{C}_{19}\text{H}_{16}\text{ClNO}_{4}$, is a nonsteroidal anti-inflammatory drug (NSAID) used for the treatment of pain. Molecular structure of indomethacin is shown in figure 2(a). Up to the present several papers
reported THz absorbance spectra of glassy and crystalline indometacine [5-7]. In refs. 5 and 6, THz absorbance spectra of glassy indomethacine were reported below 75 cm⁻¹ ~ 2.2 THz. The gradual increase of absorbance with the increase of frequency was observed, while no peak was observed in glassy samples. Very recently the high frequency limit was extended up to 6 THz by the use of a GaP THz signal generator [7]. The broad peak near 3 THz was reported in the absorbance spectrum of glassy indomethacine using the mixed pellet with polyethylene, while the complex dielectric constant was not reported.

![Molecular structures of (a) indomethacine and (b) ketoprofen.](image)

**Figure 2.** Molecular structures of (a) indomethacine and (b) ketoprofen.

In the present study, the thin plate of glassy indomethacine was prepared by melt-quenching method in liquid nitrogen. Since polyamorphic nature was reported for indomethacine, and the present glass was prepared from the γ-form crystalline powders [5]. In contrast to previous THz studies, the pellet mixed with polyethylene powder was not used. Therefore, the determination of real and imaginary parts of dielectric constant is possible by the transmission measurement. The real and imaginary parts of complex dielectric constant spectra were observed as shown in figure 3 in the frequency range from 0.5 to 6.5 THz. The real part of dielectric constant shows the step-wise decrease with the increase of frequency and the broad and asymmetric peak of the imaginary part near $\nu_1$=3 THz.

![Real and imaginary parts of THz complex dielectric constant of glassy-indomethacine melt quenched from the γ-form.](image)

**Figure 3.** Real and imaginary parts of THz complex dielectric constant of glassy-indomethacine melt quenched from the γ-form.
As the common nature of the low-energy dynamics of glassy materials, a boson peak has been observed as a broad and asymmetric peak at few THz by Raman scattering, far-infrared spectroscopy, neutron and X-ray inelastic scattering [4, 8]. It reflects the vibrational density of states (VDOS) and the broad peak has been also observed in the temperature dependence of $C_p/T^3$ curve at low temperatures, where $C_p$ is the heat capacity. It has been known that the boson peak frequency has the strong correlation with the shear modulus [8], and the molecular dynamical simulation predicted recently that the origin of the boson peak is the Ioffe-Regal limit of transverse acoustic mode, and its frequency is proportional to shear modulus [9].

The broad and asymmetric features of the peak of imaginary part near 3 THz looks like a boson peak, while considering the small shear modulus of organic glasses, the boson peak frequency can be less than 1 THz. Very recent study of glassy indomethacine by inelastic X-ray scattering reported that the Ioffe-Regal limit is about 0.6 THz [10]. As a general trend, a strong glass shows an intense boson peak and a weak fast relaxation process in an inelastic scattering spectrum, while a fragile one shows a weak boson peak and an intense fast relaxation process [11]. Since the large value of fragility index of indomethacine, $m=60-79$, was reported, the weak intensity is expected for a boson peak. Probably it is the reason why we cannot observe the boson peak in the imaginary part of dielectric constant in the present experiment. Considering the fact that the broad peak at 3 THz does not appear in the spectra of a crystalline state, it can be attributed to the some kind of vibrational mode with the distribution of mode frequency reflecting the distribution of bond length and bond angle in glassy structure and the high damping factor caused by the quenched glassy disordered structure. One possible origin of this peak is the vibration of the hydrogen bonding between molecules.

3.2. Comparison between Raman and THz spectra of crystalline racemic ketoprofen

Racemic ketoprofen, (RS)-2-(3-benzoylphenyl) propanoic acid with chemical formula $C_{16}H_{14}O_3$ is a nonsteroidal anti-inflammatory drug (NSAID) used for the treatment of inflammation and pain. Molecular structure of ketoprofen is shown in figure 2(b). It contains a chiral center at the $\alpha$-carbon to the carboxyl function and R(−) and S(+) enantiomeric forms are available [12]. Ketoprofen is polymorphic, and nine conformers were known [13]. The Raman scattering spectrum of the present sample is assigned to “conformer A” according to the experimental and calculated mode frequencies reported in ref. 13. A THz spectrum was measured using a pure pellet without mixing polyethylene.

![Figure 4. Raman scattering and THz-TDS absorbance spectra of crystalline racemic ketoprofen.](image-url)
The comparison between THz-TDS and Raman scattering spectra in the frequency range from 0.5 to 6.5 THz was shown in figure 4. In a Raman spectrum, the peaks above 100 cm$^{-1}$ such as 110, 124, 138, 157, 170 cm$^{-1}$, etc. are in agreement with the calculated values of the conformer A reported in ref. 13 within experimental uncertainty. For the internal vibrational modes above 400 cm$^{-1}$ (=12 THz), it was reported that the mode frequencies observed by Raman scattering and FTIR spectroscopy were in agreement within experimental uncertainty. In contrast, the external modes below 3 THz, the discrepancy of peak frequencies was clearly observed between THz-TDS and Raman scattering spectra as shown in figure 4.

When the point symmetry of a crystal has a center of symmetry, the mutual exclusion principle holds between Raman and IR activities. Some vibrational modes are only Raman active, while others are only IR active. According to the previous report, the most of mode frequencies observed by Raman and FTIR measurements are in good agreement above 400 cm$^{-1}$ (12 THz). Therefore, the exclusive principle seems to do not hold for internal vibrational bands above 400 cm$^{-1}$. However, below 3 THz the exclusion principle clearly holds between Raman scattering spectroscopy and THz-TDS. Consequently, for a racemic crystalline state, the exclusive principle holds below 3 THz for external vibrational modes which include translational and rotational motions, while it may not hold above 6 THz for internal vibrational modes which are defined by the internal coordinates used to describe conformation and geometry of a molecule [13]. These facts suggest that the centrosymmetric crystal lattice with translational symmetry is formed for the center of mass of molecules, while the orientation and structure of molecule at a lattice point has some kinds of disorder in crystalline racemic ketoprofen. This kind of disorder may have some similarity to an orientational glass state such as metastable glassy crystal of ethanol (crystal-II) at low temperatures [14,15]. Orientational glass is a molecular solid in which translational symmetry coexists with the static disorder of some rotational degree of freedom.

For the characterization of polymorphic and polyamorphic drug materials, it is very important to measure both THz-TDS and low-frequency Raman scattering. The two methods have the complimentary selection rules which enable the full information on vibrational properties related to the crystalline structure, glassy intermediate range order, and their strength of intermolecular interactions.

4. Conclusion
Two non-destructive spectroscopic methods - broadband THz-TDS and low-frequency Raman scattering - were employed to elucidate the vibrational properties of glassy and crystalline drug materials. The glassy-indomethacine melt-quenched from the γ form crystalline powder was measured by the broadband THz-TDS in the frequency range from 0.5 to 6.5 THz. The complex dielectric spectrum of glassy-indomethacine shows the broad peak of the imaginary part in the vicinity of 3 THz. It can be attributed to not a boson peak related to vibrational density of states but a diffusive normal mode with the frequency distribution and high damping reflecting the glassy disordered structure. The possible origin of this band is the weak interaction between molecules such as a vibration of hydrogen bond between molecules. In crystalline racemic ketoprofen, the difference between THz transmission and low-frequency Raman scattering spectra was clearly observed below 3 THz, and it suggests that the exclusive principle of IR and Raman selection rules holds for external vibrational modes of a present crystalline state. However, according to the experimental results in literature, the exclusive principle may not hold for internal vibrational modes above 12 THz. These facts indicate that a crystalline state of racemic ketoprofen has a crystal lattice with the center of symmetry while the structure of molecules at lattice points is disordered. It is suggested that for the study of polymorphic and polyamorphic states the measurements of both THz-TDS and low-frequency Raman scattering are important to give new insights into their structure and dynamics.
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References

[1] Kojima S, Tsumura N, Wada Takeda M and Nishizawa S 2003 Phys. Rev. B 67 035102
[2] Shibuya T, Suizu K and Kawase K, 2010 Appl. Phys. Express 3 082201
[3] Bartels A, Hudert F, Janke C, Dekorsy T and Köhler K 2006 Appl. Phys. Lett. 88 041117
[4] Kojima S 1993 Phys. Rev. B 47 2924
[5] Strachan C J, Rades T, Newnham D A, Gordon K C, Pepper M and Taday F 2004 Chem. Phys. Lett., 390 20
[6] Strachan C J, Taday P F, Newnham D A, Gordon K C, Zeitler J A, Pepper M and Rades T 2005 J. Pham. Sci. 94 837
[7] Otsuka M, Nishizawa J, Fukura N and Sasaki T 2012 J Infrared Milli Terahz Waves 33 953
[8] Kojima S, Matsuda Y, Fukawa Y, Kawashima M, Moriya Y, Yamada T, Yamamuro O and Kodama M 2010 J. Non-Crys. Solids 356 2524
[9] Shintani H and Tanaka H, 2008 Nat. Mater. 7 870
[10] Pogna E A A, Rodríguez-Tinoco C, Krisch M, Rodríguez-Viejo J, and Scopigno T 2013 Sci. Rep. | 3 : 2518 | DOI: 10.1038/srep02518 4
[11] Sokolov A P, Roessler E, Kiskiuk A and Quitman D 1993 Phys. Rev. Lett. 71 2062
[12] Honglu Yand Ching C B 2004 Chirality 16 541
[13] Vueba M L, Pina M E, Veiga F, Sousa J J and Batista de Carvalho L A E 2006 Int. J. Pharm. 307 56
[14] Haida O, Suga H and Seki S 1977 J. Chem. Thermodynamics 9 1133
[15] Talo’n C, Ramos M A, and Vieira S 2002 Phys. Rev. B 66 012201