3P1-10

Liquid, glass and crystalline indomethacin studied by Brillouin scattering

液体、ガラス、結晶状態におけるインドメタシンのブリルアン散乱による研究

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1. Introduction

Polymorphic nature of drug materials relates to good glass-forming tendency owing to the energy landscape structure with many basins. Indomethacin (IMC) [1-(p-chlorobenzoyl)-5-methoxy- 2-methy lindole-3-acetic acid] is one of the non-steroidal anti-inflammatory drugs used for the treatment of fever, pain, and swelling. Themolecular structure of IMC is shown in Fig. 1. IMC undergoes a liquid-glass transition at the glass transition temperature, T_g = 315 K upon cooling from the melt. Therefore, a large size of transparent bulk glass is available. Currently, in the pharmaceutical research, there is a growing interest in the development of amorphous (glassy) pharmaceuticals, because they often show a better solubility than the crystalline counterpart. IMC is of particular interest [1-6].The purpose of the present study is to give new insights into the understanding of elastic properties of crystalline and glassy IMC.

2. Experimental

IMC ($C_{19}H_{16}ClNO_4$; T_m = 434 K and T_g = 315 K) crystalline powder with 99% purity was purchased from Sigma–Aldrich. The commercial product was supplied as the crystalline c-form (c-IMC) and used without further purification. The glassy state of IMC was prepared by melt-quenching of the crystalline powder c-IMC from 438 K which is slightly higher than the melting point, down to 296 K under normal atmospheric conditions.[5)]

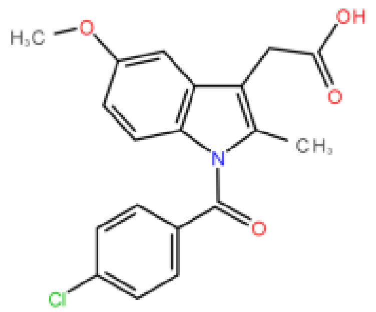

Fig. 1 Molecular structure of indomethacin.

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Brillouin scattering was measured in a backward scattering geometry using a tandem Fabry–Perot interferometer (JRS TFP-1) in combination with a reflection optical microscope (Olympus BX-60) and a single frequency green Yttrium aluminium garnet (YAG) laser (Coherent Compass 315M-100) with a wavelength of 532 nm. The spot size of the beam incident to the sample was less than 10 μm. The temperature dependence of elastic properties was measured using a heating/cooling stage (Linkam HTMS600) [7,8].

3. Results and discussion

Brillouin scattering of longitudinal acoustic (LA) mode was measured by the back scattering geometry. While, that of transverse acoustic (TA) mode was observed by backward scattering and reflection induced ΘA (RIΘA) scattering geometry [9]. Figure 2 shows the schematic illustration of RIΘA geometry in which 90° angle scattering occurs by the reflected incident beam “BC” at the bottom of a sample “B”, and we can observe both 90° and 180° angles scattering. Brillouin scattering spectra of glassy IMC measured by standard back scattering and RIΘA scattering geometry were shown in Figs. 3 (a) and (b), respectively.

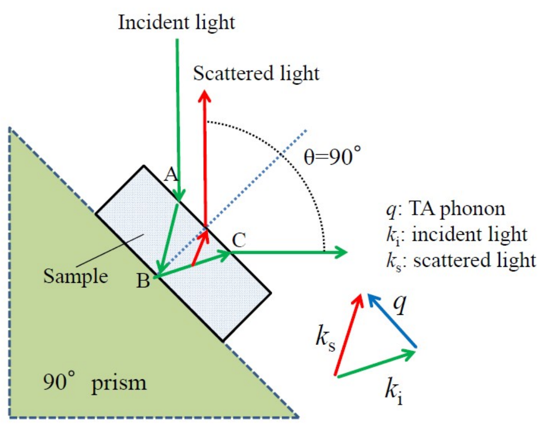

Fig. 2 Scattering geometry of reflection induced ΘA scattering.

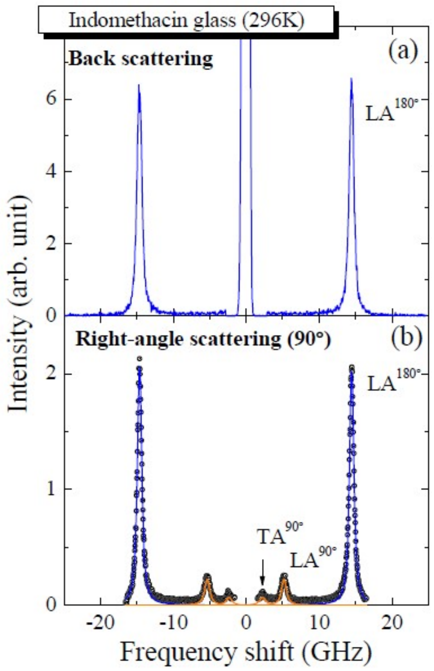

Fig. 3 Brillouin scattering spectra of glassy indomethacin in (a) backward and (b) RIΘA scattering.

The temperature dependence of frequency shift and FWHM of liquid, glass, and γ-form IMC crystal is shown in Fig. 4. Upon heating of a γ-form crystal from low temperature, the gradual decrease of the shift and the increase of FWHM due to anharmonisity were observed below T_m. A glassy sample also shows the gradual decrease of the shift and increase of FWHM below T_g. Above T_g, the remarkable decrease of the shift and the increase of FWHM were observed. However, about 30 K below T_m the crystallization occurred and no Brillouin peak was observed by devitrification. For further heating, the Brillouin peaks were clearly observed in a liquid phase above T_m.

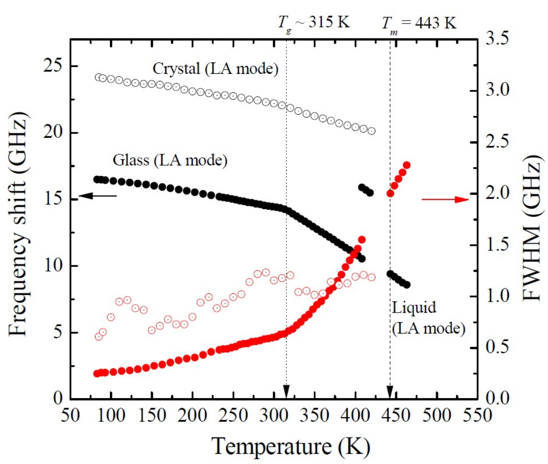

Fig. 4 Temperature dependence of frequency shift and FWHM of amorphous and crystalline indomethacin.

For a γ-form IDM crystal, elastic constants were determined as a function of temperature as shown in Fig. 5. The gradual decrease upon heating is due to the lattice anharmonicity.

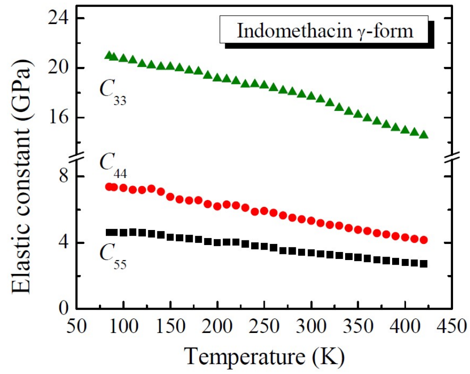

Fig. 5 Temperature dependence of elastic constants in γ-form indomethacin crystal.

4. Conclusion

The glassy state of indomethacin was successfully prepared by melt-quenching method from the crystalline powder indomethacin. Elastic properties of liquid, glass and crystalline indomethacin were studied by Brillouin scattering spectroscopy using the backward scattering and reflection induced ΘA scattering geometry. Upon heating of glassy indomethacin, the elastic anomaly of a liquid-glass transition was clearly observed at T_g. The temperature dependence of elastic constants was determined in a γ-form indomethacin crystal.

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