

“Acoustic and thermal anomalies in a liquid-glass transition of racemic *S*(+)-*R*(-) ketoprofen”

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Abstract

Acoustic and thermal properties of pharmaceutical racemic *S*(+)-*R*(-) ketoprofen were investigated in wide temperature range including glassy, supercooled liquid and liquid states by Brillouin scattering and temperature modulated DSC (MDSC). Sound velocity and acoustic attenuation exhibit clear changes at 265 K indicating a liquid-glass transition and show the typical structural relaxation above T_g . The high value of the fragility index $m = 71$ has been determined by the dispersion of the complex heat capacity. New relaxation map was suggested in combination with previous study of dielectric measurement.

Keywords: ketoprofen, glass transition, Brillouin scattering, MDSC, fragility

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1. Introduction

Glassy pharmaceuticals have attracted much attention from the viewpoint of new pharmaceutical engineering [1,2]. These materials easily undergo vitrification on cooling from the melts, and they exhibit similar properties as typical structural glasses [3-6]. However, their fundamental physical properties related to a liquid-glass transition are still unclear. Up to the present, glass forming materials with simple molecular structures were extensively studied by both experimental and theoretical approaches [7], while the understanding of glass formers with complex molecular structures is not enough. Therefore, the study of glassy pharmaceuticals is important to provide basic properties of chemical physics useful to pharmaceutical applications and to understand the dynamical properties of glass transitions on complex molecules.

Ketoprofen is one of non-steroidal anti-inflammatory drugs (NSAIDs) with good analgesic properties used in the treatment of rheumatoid arthritis and osteoarthritis. A glassy state of ketoprofen can be obtained easily and was studied by thermal [8,9] and dielectric measurements recently [10]. The temperature dependences of the α -relaxation process and the secondary γ -relaxation process were observed in the previous study [10]. Although previous dielectric measurement investigated wide frequency range from Hz to MHz, the relaxation processes in mHz and GHz ranges were not investigated in detail. Temperature modulated DSC (MDSC) can be then considered as the excellent technique to study very slow relaxation process just above glass transition temperature T_g [5,11]. Therefore, MDSC can investigate the "fragility" in glass forming materials, which classify the steepness of the temperature dependence of α -relaxation process just above T_g [5,13]. Fragility is one of the central parameters describing glass transition dynamics near T_g [14], while the determination by the thermal method is not well studied.

Brillouin light scattering has been a powerful tool to characterize acoustic properties of condensed matters in a GHz range [15]. The frequency shift and the linewidth provide the sound velocity and the acoustic attenuation of acoustic waves thermally excited in a material, respectively. Recently, acoustic properties of pharmaceutical aspirin and ibuprofen in their crystalline, glassy and liquid states were investigated by Brillouin scattering, from which acoustic anomaly across a glass transition was clearly observed [16-18]. In addition, Brillouin scattering is sensitive to the existence of intramolecular secondary relaxation which couples with acoustic phonon in a GHz range [19-21].

The purpose of this study is to prove various fundamental properties of the

anti-inflammatory drug, racemic ketoprofen, in the glassy, supercooled and equilibrium liquid states by using Brillouin scattering, MDSC and refractive index measurements. The liquid-glass transition, the acoustic behaviors, fragility and thermo-optic properties have been investigated systematically, and the new relaxation map was suggested.

Experimental

2.1. *Material*

Ketoprofen ((*RS*)-2-(3-benzoylphenyl) propanoic acid, $C_{16}H_{14}O_3$, a molar mass of 254.28 g/mol) was purchased from Sigma Co. (catalogue No. L1751 (CAS 22071-15-4), 98% GC assay). It is a racemic mixture of *S*-(+)-ketoprofen and *R*-(-)-ketoprofen (see Figure 1) and the studied (\pm)-ketoprofen mixture is referred as ketoprofen. Before starting a measurement, the ketoprofen powder was heated and kept 5 minutes at 370 K ($T_m \sim 368$ K [8,9]) to get an equilibrium liquid state. And then the liquid ketoprofen was quenched to liquid nitrogen temperature with the high cooling rate of more than 10 K/min. A glassy state of ketoprofen was easily obtained by this method, and then measured upon heating.

2.2. *Brillouin scattering*

The Brillouin scattering was measured by a micro-Brillouin scattering apparatus, which is a combination of a microscope and a Sandercock-type 3 + 3 passes tandem multipass Fabry-Perot interferometer [15]. The Brillouin spectra were measured at a backward scattering geometry using a single frequency green YAG laser with a wavelength of 532 nm. The objective lens of the microscope focuses an incident laser beam onto the sample and simultaneously collects the scattered light. An ordinary photon counting system and a multi-channel analyzer were used to accumulate the output signals. A heating/cooling stage (Linkam, THMS600) was used to control the temperature of the sample from 90 to 473 K. The temperature stability of a sample was within ± 0.1 K.

2.3. *Prism-coupling method*

In order to determine the sound velocity and acoustic attenuation, the refractive index of liquid ketoprofen was measured accurately as a function of temperature by using the Metricon Model 2010/M (Metricon), based on the prism coupling method with the degree of accuracy of ± 0.0001 . A green YAG laser with a wavelength of 532 nm was

used to measure refractive index at the wavelength same as the exciting source of Brillouin scattering measurement. The refractive index of liquid ketoprofen was measured as a function of temperature from 370 K to 423 K.

2.4. *Temperature Modulated DSC*

DSC T-zero Q200 (TA Instruments, Tokyo, Japan) equipped with Liquid Nitrogen Cooling System was used to measure a complex heat capacity, $C_p^* = C_p' - iC_p''$. Before measurements, we performed the calibrations to measure accurate data. Baseline calibration also has been done through the entire temperature range used in the experiments, and heat capacity calibration has been performed by using a sapphire disk as a standard. Temperature calibration has been done to examine the heat of fusion of Indium. A sample was put into an aluminum pan, and the mass of each sample was about 10.0 mg. In the measurement, sample pan was heated over T_g with the temperature control procedure; linear heating rate was 0.5-1.0 K/min, temperature modulation amplitude was ± 1.0 K, and temperature modulation frequency was from 5 to 50 mHz. Dry nitrogen was flowed in the sample chamber as a purge gas with the flow rate of 20 ml/min during the experiments. Details about MDSC and data analysis are written in ref [5, 11-13].

2. Results and discussion

3.1. *Brillouin scattering*

Figure 1 shows the typical Brillouin scattering spectra of glassy, supercooled liquid, and liquid states ketoprofen collected during heating. For all spectra, the Brillouin doublet corresponding to the longitudinal acoustic mode (LA mode) can be seen and the transverse acoustic mode (TA mode) does not appear from the backward scattering geometry. At a high temperature liquid state, a quasi-elastic scattering so-called central peak can be seen in addition to Brillouin doublet. On heating from 80 K, LA mode shows markedly softening over the entire temperature range, while the LA width shows continuous increase reflecting a relaxation process. Above T_g , supercooled liquid of ketoprofen has never been recrystallized during heating measurements of Brillouin scattering. No recrystallization was also observed by calorimetric measurement [9]. It is a special feature of ketoprofen molecules in contrast to the fact that representative NSAIDs such as aspirin exhibit strong tendency of recrystallization [3,16]. The correlation between the glass formation and the number of polymorphic modifications

was reported in chalcogenide and other glassy systems by B. N. Blinov [22]. It was shown that this correlation can be explained in terms of the thermodynamics criterion for glass-forming ability. The polymorphism of aspirin was studied and two crystal structures were reported by P. Vishweshwar. et al.[23]. Therefore, aspirin exhibits strong crystallization tendency because of the low polymorphic nature. On the other hand, the existence of nine deferent geometries was reported by the density functional theory (DFT) calculation as the energy minimum conformations in crystalline states of ketoprofen [24]. Consequently, ketoprofen shows the low crystallization tendency in contrast to other NSAIDs.

To investigate acoustic properties, Brillouin spectra were fitted by using the superposition of the Lorentzian functions convoluted by the Gasssian instrumental function of the interferometer, resulting in the Voigt spectral function. From this fitting process, the Brillouin frequency shift (ν_B) and full width at half maximum (FWHM, Γ_B) of each spectrum were obtained as a function of temperature. From the ν_B and Γ_B of obtained spectra, we calculated the longitudinal sound velocity V and acoustic attenuation α of glassy, supercooled liquid and liquid states of ketoprofen by using the following equations (1) and (2),

$$V = \frac{\lambda_0 \nu_B}{2n \sin(\frac{\theta}{2})} , \quad (1)$$

$$\alpha = \frac{\pi \Gamma_B}{V} , \quad (2)$$

where n is the refractive index of ketoprofen as described in the following section, λ_0 is the wavelength of incident beam (532 nm) and θ is scattering angle (180°), respectively. Figure 2 shows the temperature dependences of the sound velocity and the acoustic attenuation. In a glassy state, the sound velocity decreases, while the attenuation increases gradually on heating from 80 K. At these low temperatures near T_g , the α -relaxation frequency is lower than 1 Hz. Therefore there is little contribution from it for the acoustic attenuation in a GHz range. However, it has a finite value below T_g caused by the coupling of LA mode with internal, molecular degree of freedom, i.e., anharmonicity of a solid state. On further heating, sound velocity and acoustic attenuation show the drastic change of the slopes at ~ 265 K, indicating the occurrence of a liquid-glass transition. We determine this temperature as T_g , which is in good agreement with dielectric T_g (267 K) and calorimetric T_g (270 K) in literatures [8-10].

Above T_g , we obtained whole acoustic data of supercooled liquid ketoprofen without recrystallization. There are two well know features expected in the presence of the structural relaxation process. (I): A marked dispersion of the sound velocity is accompanied by a maximum of the acoustic attenuation around 430 K corresponding to the coupling between the relaxation rate and characteristic frequency of acoustic phonon. (II): The sound velocity decreases markedly in a supercooled liquid state and the rate of decrease becomes smaller with further heating in a liquid state corresponding to the relaxed sound velocity V_o . Similar changes of the sound velocity and acoustic attenuation across a glass transition were observed in simple glass-forming materials such as ethanol, propylene glycol by Brillouin scattering [19,20].

From these experimental results, the relaxation time was determined by the following equation (3) under the assumption of a single relaxation process (Debye model) [25]

$$\tau(T) = \frac{1}{2\pi(\Gamma_B - \Gamma_\infty)} \frac{v_B^2 - v_0^2}{v_B^2}, \quad (3)$$

where v_0 is relaxed frequency shift and Γ_∞ is unrelaxed FWHM. Figure 3 shows the temperature dependence of relaxation time. In liquid and supercooled liquid states, the plot is essentially linear, indicating that $\tau(T)$ obeys the Arrhenius law approximately:

$$\tau(T) = \tau_0 \exp\left(\frac{\Delta E}{RT}\right), \quad (4)$$

where τ_0 , ΔE and R are pre-exponential factor, a activation energy, and gas constant, respectively. Activation energy and pre-exponential factor were determined from the slope of the liner fitting line as $\Delta E = 22.9$ (kJ/mol), $\tau_0 = 3.58 \times 10^{-14}$ s.

In comparison with the dielectric measurement, we add the values reported in ref. 10 in Figure 3. The temperature dependence of α -relaxation time was fitted by Vogel-Fulcher-Tammann (VFT) equation,

$$\tau_\alpha = \tau_0 \exp\left(\frac{DT_0}{T - T_0}\right), \quad (5)$$

where T_0 , τ_0 , and D are fitting parameters. The parameters of the reported VFT are $T_0 = 213.89$ K, $\log(\tau_0/s) = -15.19$, and $D = 9.84$ [10]. We tried to extrapolate the fitting line described by VFT equation toward to high temperature, but α -relaxation time does

not become comparable to our obtained process. However, the deviation of the VFT equation from plots can be seen in a high temperature range above 330 K. Moreover, for the most of glass formers, it is known that at a crossover temperature T_{cross} in the temperature range $T_{cross} \approx (1.1-1.2) T_g$, the temperature dependence of α -relaxation time shows the crossover from a low temperature VFT equation to a high temperature one [4, 26-28]. Therefore, we roughly estimate a crossover temperature $T_{cross} = 320$ K ($1.2 \cdot T_g$) and add a new reasonable VFT₂ equation line for high temperature behavior above T_{cross} in addition to the reported one. Here, the parameters of the VFT₂ equation are $T_0 = 228.4$ K, $\log(\tau_0/s) = -13.7$, and $D = 6.61$. As shown in Figure 3, VFT₂ becomes comparable to our observed process. In this case, the observed process seems to internal relaxation process caused by the bifurcation from α -relaxation at high temperatures.

In addition, the dielectric γ -relaxation was observed at low temperatures and its Arrhenius parameters were reported as $\Delta E = 37.9$ (kJ/mol), $\tau_0 = 7.24 \times 10^{-14}$ s [10]. Compared to γ -relaxation, activation energy of the relaxation process obtained by Brillouin scattering is about a half. Therefore, we defined the relaxation process as δ -relaxation shown in Figure 3. The smaller activation energy of δ -relaxation process probably originated from intramolecular motion of a smaller part of ketoprofen. Possible origin of the δ -relaxation processes is the internal degree of freedom such as $-\text{CH}_3$ rotation or phenyl-ring-flip motions [22]. Considering the origin of this process, the δ -relaxation process may still remain in a glassy state.

Refractive index

The temperature dependence of the refractive index of liquid ketoprofen over the temperature range between 370 K (T_m) and 423 K was shown in Figure 4. Obtained values were fitted by assuming a linear equation given by

$$n(T) = -3.794 \times 10^{-4} T + 1.718 \quad , \quad (6)$$

The temperature dependence of refractive index in a supercooled liquid state was evaluated by using eq. (6). And we assumed the refractive index in a glassy state to be constant, $n(T \leq T_g) = 1.617$, which is the extrapolated value at T_g ($= 265$ K, defined by Brillouin scattering) from the eq.(6), because the thermo-optic coefficient dn/dT in a glassy state is usually very small [29,30]. Then, the sound velocity and the acoustic attenuation were calculated in whole temperature range.

Physically more relevant information can be obtained from our experimental results. Assuming the Lorentz-Lorenz relation, the function $f_{LL} = (n^2 + 2)/(n^2 - 1)$ is

proportional to specific volume and is linear in various temperature ranges if no phase transition exists [31,32]. The temperature dependence of f_{LL} is shown in Figure 4. From the linear fitting by the following equation (7), the thermal expansion coefficient β can be directly obtained as $\beta = a/b$.

$$f_{LL} = \frac{n^2+2}{n^2-1} = aT + b = 1.68 \times 10^{-3} T + 2.394 , \quad (7)$$

The volumetric thermal expansion coefficient of a liquid ketoprofen was determined as $7.018 \times 10^{-4} \text{ (K}^{-1}\text{)}$. The values of β of pure water and ethanol are $2.38 \times 10^{-4} \text{ (K}^{-1}\text{)}$ and $10.3 \times 10^{-4} \text{ (K}^{-1}\text{)}$ [33]. The smaller value of water is related to the intermolecular force, such as formation of hydrogen bonded tetrahedral network of water molecules. In ketoprofen, the value of β is slightly larger than that of *S*-(+)-ibuprofen ($\beta = 6.049 \times 10^{-4} \text{ (K}^{-1}\text{)}$) [18], so it seems that intermolecular force of ketoprofen is slightly weaker than that of *S*-(+)-ibuprofen.

3.2. Complex heat capacity

Figure 5 shows the real and imaginary parts of the complex heat capacity of ketoprofen for some investigated frequencies. The C'_p shows the step-wise change and C''_p has a peak. These behaviors are typical features of the complex susceptibility of a relaxation process. The peak temperature (T_ω) of C''_p shifts to higher temperature as the modulated frequency f become higher. T_ω is the temperature corresponding to the coupling between the relaxation rate and characteristic frequency of modulated temperature and then the temperature dependence of $\tau(T_\omega)$ can be given by,

$$\tau(T_\omega) = \frac{1}{2\pi f} = \frac{1}{\omega} , \quad (8)$$

where ω is the angular frequency of the temperature modulation [5,13]. The temperature dependence of α -relaxation time determined from each C''_p is shown in Figure 3. The calorimetric T_g , at which the α -relaxation time is 100 s, was deduced from the MDSC experiments to be 266 K. The determination of T_g enabled us to calculate the fragility index m by using eq.(9),

$$m = \lim_{T \rightarrow T_g} \left| \frac{d(\log \tau(T))}{d(T_g/T)} \right| , \quad (9)$$

For ketoprofen, we find $m = 71$ which is a typical value of a fragile glass former. However, the fragility index obtained by MDSC is slightly smaller than that value determined from dielectric spectroscopy ($m = 86.57$) [10]. The difference between thermal and dielectric relaxation time of α -relaxation was observed in some researches and discussed [6,11]. We consider that the difference is caused by the following reasons. Firstly, the physical meaning is different between thermal relaxation and dielectric relaxation. Thermal relaxation involves all degrees of freedom of molecular motions, such as local or overall changes in the configuration. On the other hands, dielectric relaxation involves only the modes of polar motions in which dipole moments change and does not include any nonpolar motions. Molecular motions in a supercooled liquid state involve a variety of nonpolar motions. Therefore, the α -relaxation times measured by calorimetric and dielectric measurements may differ as well as the value of m . Secondly, in the dielectric measurement the fragility was determined from the extrapolation of VFT equation line from the frequency higher than that of MDSC. Therefore, the observed values of fragility index determined by MDSC and dielectric measurements show some difference.

As shown in Figure 3, relaxation process in mHz and GHz range were obtained and new relaxation map was suggested in combination with previous study of dielectric measurement. Since molecular mobility is one of main concern of glassy pharmaceuticals [1,2], these information will aid for further study and drug design.

3. Conclusion

Various fundamental properties of the anti-inflammatory drug, racemic ketoprofen, in the glassy, supercooled and equilibrium liquid states were investigated by using Brillouin scattering, MDSC and refractive index measurements. No crystallization was observed in a supercooled liquid state, because of the high polymorphic nature of ketoprofen. Temperature dependences of the sound velocity and acoustic attenuation exhibit clear changes in their slopes at 265 K indicating the occurrence of a liquid-glass transition and show the typical features expected in the presence of the structural relaxation process above T_g . The remarkable change of complex heat capacity was observed in the vicinity of T_g by MDSC. From the frequency dependence of C''_p , the fragility index was obtained to be $m = 71$ which indicates the typical fragile nature of a liquid-glass transition of ketoprofen. Comparison of fragility index obtained by dielectric spectroscopy indicates the difference of thermal relaxation and dielectric one.

Relaxation processes in mHz and GHz range were obtained and new relaxation map was suggested in combination with previous study of dielectric measurement. The temperature dependence of refractive index was measured from 370 K to 423 K at 532 nm, from which thermo-optic coefficient dn/dT , and thermal expansion coefficient β were also determined accurately. The observed basic properties of chemical physics will give new insights into pharmaceutical applications and glass transition dynamics of complex molecules.

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Figure captions

Figure 1. Temperature dependence of Brillouin scattering spectra at backward scattering geometry. Inset is molecular structure of ketoprofen, where C* is a chiral carbon atom.

Figure 2. Temperature dependence of sound velocity and acoustic attenuation derived from Brillouin spectra.

Figure 3. Arrhenius plot of relaxation times determined by Brillouin scattering, MDSC and dielectric measurement in ref. 10. Temperature dependence of α -relaxation time was fitted by VFT equations (blue solid line is reported VFT and red dotted-dashed line is VFT₂). Temperature dependences of secondary relaxations, γ and δ were fitted by Arrhenius equations (dashed lines).

Figure 4. Temperature dependence of refractive index and $f_{LL} = (n^2 + 2)/(n^2 - 1)$ of ketoprofen.

Figure 5. The temperature dependence and frequency dependence of the complex heat capacity.

Graphical abstract: Arrhenius plot of relaxation times of ketoprofen

Figure 1

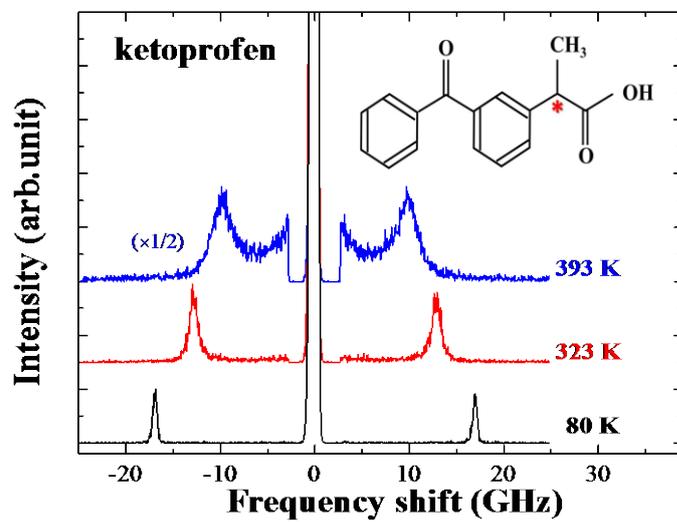


Figure 2

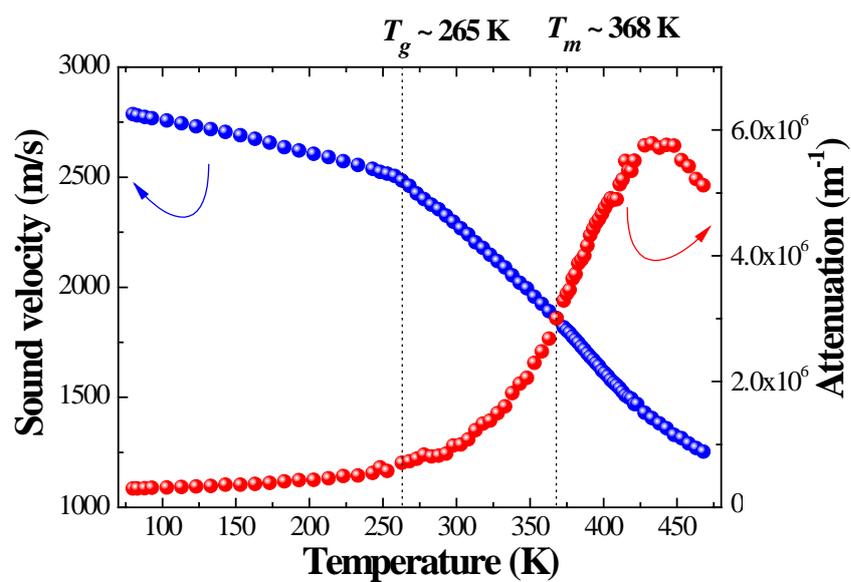


Figure 3

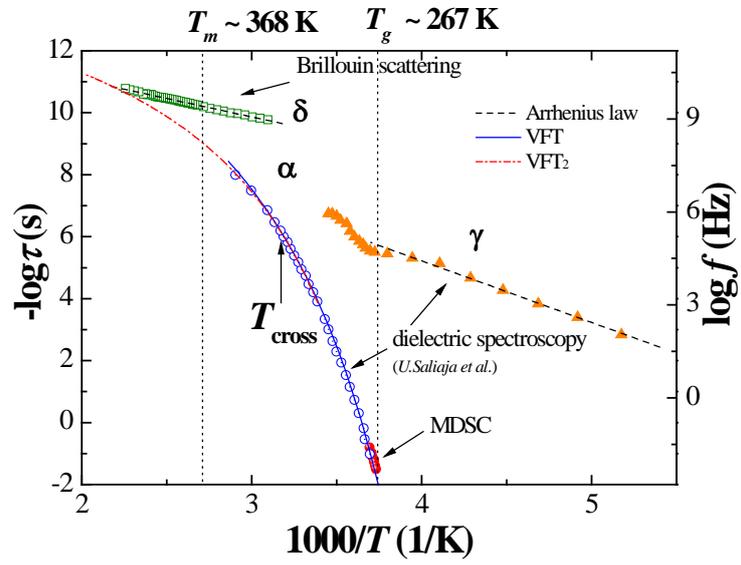


Figure 4

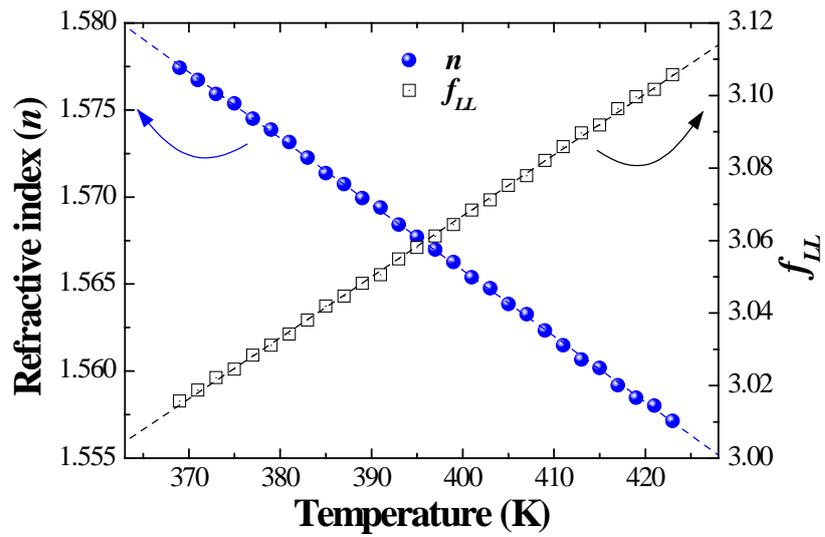
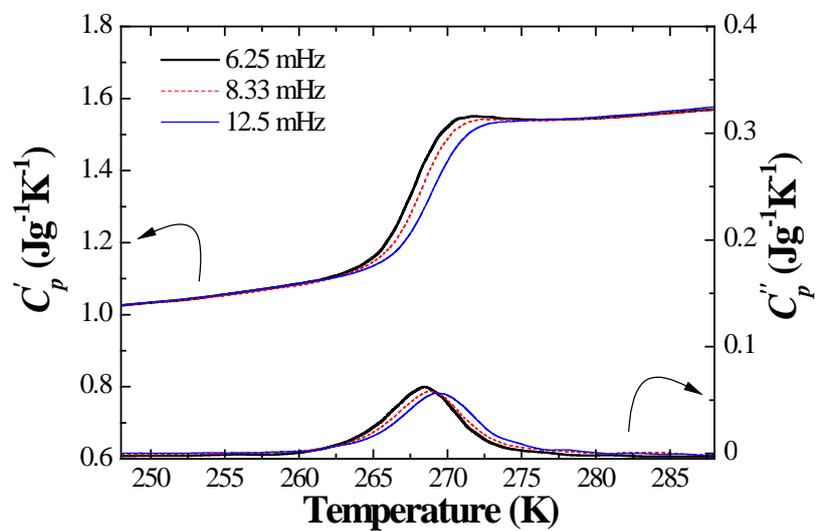


Figure 5



Graphical abstract

