Relaxation and Crystallization of Amorphous Carbamazepine Studied by Terahertz Pulsed Spectroscopy

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Received 30 November 2006; revised 16 January 2007; accepted 22 January 2007

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.20908

ABSTRACT: At the example of carbamazepine the crystallization of a small organic molecule from its amorphous phase was studied using *in situ* variable temperature terahertz pulsed spectroscopy (TPS). Even though terahertz spectra of disordered materials in the glassy state exhibit no distinct spectral features we demonstrate subtle changes in the spectra with increasing temperature and discuss the findings in respect to the density of vibrational states. The crystallization leads to distinct spectral features allowing the crystallization and subsequent polymorphic phase transition at higher temperatures to be studied in detail. It is possible to study both relaxation and crystallization processes by variable temperature TPS. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 96:2703–2709, 2007

Keywords: terahertz pulsed spectroscopy (TPS); crystallization; amorphous; carbamazepine; phase transition; far infrared

INTRODUCTION

The development of photoconductive antennas switched by femtosecond lasers as new light sources for spectroscopy in the far-infrared region has lead to a renaissance in experimental work in this part of the electromagnetic spectrum.[1] Utilizing the coherent properties of the broadband pulsed radiation generated by these antennas the instruments can be operated at room temperature without the need of cryogenic detection. Both amplitude and phase information can be directly recovered as a signal directly proportional to the electric field of the terahertz pulse E_{THz}, rather than just the field intensity, is measured using a coherent detection scheme.

$$\frac{E_{\mathrm{THz,s}}}{E_{\mathrm{THz,r}}} = T(n)\,\exp\left(-\frac{\alpha d}{2}+\frac{in\omega d}{c}\right) \qquad (1)$$

Here, $T(n)$ is the Fresnel reflection loss, α the absorption coefficient, d the sample thickness, n the refractive index, $\omega = 2\pi f$ the angular frequency of the radiation where f is the frequency of the radiation, c the speed of light in vacuum, and the indices s and r denote the sample and reference, respectively. With the current generation of instruments the spectral range from 2 to 130 cm^{-1} (60 GHz to 4 THz) can be accessed.[2] To distinguish this type of spectroscopic setup from traditional far-infrared spectroscopy the term terahertz pulsed spectroscopy (TPS), sometimes also referred to as terahertz time-domain spectroscopy (THz-TDS), is used.

In crystalline materials radiation at terahertz frequencies is in resonance with translations and liberations of the molecules in the crystalline

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Journal of Pharmaceutical Sciences, Vol. 96, 2703–2709 (2007)

lattice as well as low-energy transitions within a molecule such as bending and torsion vibrations. These properties make terahertz spectroscopy ideal for the study of intermolecular vibrations and hydrogen bonding networks. Several studies have highlighted the potential of this technology for the characterization of organic molecular crystals.[3–8] The advantage of very fast spectral acquisition in TPS allows the study of the mechanism and dynamics of solid-state phase transitions and dehydration processes.[9–11]

Along with the advances in experimental work at terahertz frequencies the theory to interpret the recorded spectral features has made considerable progress. Starting from density functional theory (DFT) calculations of isolated molecules, where the agreement between theory and experiment was found to be very poor, the field has been evolving and it is now commonly acknowledged that the solid-state environment needs to be included into the calculations of the electronic structure. Using periodic boundary conditions for calculations with either force-field or DFT approaches it is possible to make assignments of the spectral features observed in the terahertz range.[12–16] However, the calculations are either computationally very expensive, as is the case for the DFT calculations, or the assignments are very tentative, as is the case for the force-field calculations. No optimal approach has been described yet that could be used on a routine basis.

Apart from the work on crystalline structures in small organic molecules, the terahertz spectra of the amorphous phase of glucose and indomethacin have been reported.[4,6] Based on data from molecular dynamics calculations as well as experimental terahertz spectra and inelastic neutron scattering data of inorganic glasses a theory on the frequency dependence of the absorption coupling coefficient between photons in the far infrared and the atomic vibrations in the amorphous phase has been presented recently.[17]

The amorphous state has attracted a strong interest in the pharmaceutical sciences as novel drug compounds generally tend to exhibit solubility problems that could possibly be overcome by administrating the drug to the patient in its amorphous form.[18–20] However, there is still a lack of understanding of the fundamental physics and the general material properties of disordered materials.[21–25]

In this study, we explore how TPS can be used to study relaxation processes with increasing temperature in disordered carbamazepine, a drug used for the treatment of epilepsies. We follow the spectral changes in the terahertz spectra during the transition from the glassy into the rubbery state—leading to its crystallization and subsequent phase transition.

MATERIALS AND METHODS

Carbamazepine (CBZ, 5H-dibenz[*b*,*f*]azepine-5-carboxamide, USP grade) was obtained from Sigma–Aldrich (Poole, UK) and used as received. For the preparation of the amorphous form 5 g of the polycrystalline material were placed in an aluminum beaker and heated above its melting point on a hot plate. The melt was quench cooled in liquid nitrogen. In an agate mortar the resulting amorphous CBZ was gently ground into smaller particles. Using a 13 mm die press (Specac, Orpington, UK) 250 mg amorphous CBZ was compressed directly at a load of 2 tons into a pellet.

The measurements were performed in a variable temperature cell (Specac) as described previously.[9] Here, the sample was heated from 293 K to its melting temperature at a rate of 1 K/min and spectra were continuously acquired every 15 s using a TPS spectra1000V spectrometer (TeraView, Cambridge, UK) set to a spectral resolution of 1.5 cm^{-1} over the range of 2–70 cm^{-1}. Three hundred scans were coadded for each spectrum and Blackman-Harris 3-term apodization was applied for the Fourier transformation. Sample spectra were referenced against the spectrum of the empty sample holder and absorbance spectra were calculated. The sample compartment of the spectrometer was purged with dry nitrogen gas throughout the experiment.

RESULTS AND DISCUSSION

The contour plot of Figure 1 provides an overview of the spectral changes observed by TPS during the heating of the amorphous sample pellet through its glass transition temperature into the rubbery state, the crystallization as form III and its conversion into form I just below its melting temperature.

Initially, the spectrum of the amorphous phase exhibits increasing absorbance with increasing wavenumbers. No distinct spectral features can be detected (Fig. 2A). These findings are similar to the spectra of other amorphous small molecule