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Direct measurement of molecular mobility and crystallisation of amorphous pharmaceuticals using terahertz spectroscopy☆

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ABSTRACT

Despite much effort in the area, no comprehensive understanding of the formation and behaviour of amorphous solids has yet been achieved. This severely limits the industrial application of such materials, including drug delivery where, in principle, amorphous solids have demonstrated their great usefulness in increasing the bioavailability of poorly aqueous soluble active pharmaceutical ingredients. Terahertz time-domain spectroscopy is a relatively novel analytical technique that can be used to measure the fast molecular dynamics of molecules with high accuracy in a non-contact and non-destructive fashion. Over the past decade a number of applications for the characterisation of amorphous drug molecules and formulations have been developed and it has been demonstrated how this technique can be used to determine the onset and strength in molecular mobility that underpins the crystallisation of amorphous drugs. In this review we provide an overview of the history, fundamentals and future perspective of pharmaceutical applications related to the terahertz dynamics of amorphous systems.

Contents

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1. Introduction

With the development of terahertz time-domain spectroscopy (THz-TDS) in the 1970s and 1980s [1–5] a completely new technology has been established to study molecular excitations in the far-infrared, here commonly referred to as $0.1-4$ THz or $3-130$ cm^{-1}, with corresponding photon energies of $0.4-16$ meV. Electromagnetic radiation at terahertz frequencies strongly interacts with systems that have characteristic energetic transitions at meV energies and lifetimes on picosecond time-scales. This includes phonons in crystalline solids, transient molecular dipoles, relaxational dynamics in aqueous liquids, hydrated biological matter and weakly bonded systems such as hydrogen-bonded networks and Van der Waals interactions, amongst others. A useful recent review including an extensive list of relevant references can be found in [6] and a more detailed review of the developments in spectroscopy is found in [7].

The unique fingerprints of crystalline materials at terahertz frequencies, which originate from the inter-molecular low frequency coherent motions, make terahertz spectroscopy a very sensitive technique in the differentiation of crystalline polymorphs [8,9], hydrates [10,11] and cocrystals [12,13] and also allow the observation of phase transitions between such solid state modifications. While it is far from trivial to assign these spectral features (which represent complex inter-molecular motions that are often coupled with low energy intra-molecular modes), to specific vibrational modes using resource intensive computational techniques, it was immediately obvious how the sensitivity of the fingerprint spectra to the solid state structure could be exploited for the characterisation of active pharmaceutical ingredients (API): i) the insensitivity of THz-TDS to thermal interference allows measurements of materials and processes to be acquired over a wide range of temperatures; ii) performing time-resolved studies on the sub-picosecond time-scale potentially allowing insight into dynamic systems such as amorphous systems; and iii) the low energy used in terahertz spectroscopy minimises the risk of sample degradation [8,14]. As a consequence there has been considerable interest in the study of crystalline solids ever since THz-TDS was introduced to pharmaceutical analysis 10–15 years ago.

In contrast, owing to the fact that the absorption spectra of all amorphous materials exhibit only a monotonically increasing spectral baseline with the absence of any characteristics peaks, the analysis of amorphous solids using THz-TDS has initially received much less attention. However, significant progress was made over the last five years in understanding the critical role that terahertz dynamics play in characterising amorphous solids in a pharmaceutical context and beyond. Consequently, there are exciting opportunities to use terahertz spectroscopy to study amorphous materials, and these are the focus of this review.

2. Exploration of terahertz dynamics prior to THz-TDS

2.1. Poley absorption

The study of the dynamics of disordered systems that occur at terahertz frequencies predate the development of modern THz-TDS which dominates experimental investigations today. Probably the earliest theoretical prediction of the existence of terahertz absorption in non-crystalline materials was made in 1955 by Poley in his study of low viscosity polar liquids using dielectric measurements and optical spectroscopy [15]. Poley realised that there was a mismatch between the dielectric constant $\varepsilon_{\mathrm{inf}}$, as measured in the microwave region, when extrapolated into the far-infrared and the estimated refractive index squared n^2 in the microwave region based on measurements at visible and infrared frequencies. Given this discrepancy, Poley hypothesised that an additional region of dipolar absorption must exist at terahertz frequencies in liquids. Since experimental data have proved this to be the case, the term Poley absorption has frequently been used to describe this observation [16].

2.2. Far-infrared spectroscopy

In terms of experimental measurements, the first terahertz absorption spectra were reported a couple of decades later by using Fourier transform infrared spectroscopy (FTIR). FTIR experiments on samples of inorganic glasses that differed in their electronic and structural properties showed that a universal absorption feature existed at terahertz frequencies which was universal and independent of temperature. It was found to increase in intensity with frequency as ν^{β} ($\beta \lesssim 2$) [17]. The frequency-squared dependence of absorption resembles that of a vibrational density predicted by Debye theory. It was therefore concluded that the physical nature of the feature was due to disorder-induced coupling of the far-infrared radiation to a density of low-frequency Debye modes.

Of particular importance in this context are the dielectric and FTIR studies reported by Reid and Evans in the late 1970s and early 1980s [18]. By this time the dielectric spectroscopy community was well aware of the existence of two universal dielectric relaxation mechanisms: the primary (α-) and the secondary (Johari-Goldstein β-, JG-β) relaxation processes [19]. Based on the FTIR studies performed on supercooled liquids and glasses of solutions of decalin a third universal absorption feature was observed at terahertz frequencies. In analogy to the terminology used by the dielectric spectroscopy community Reid and Evans called this feature a γ process [18]. It is tempting to compare this so-called γ process and the Debye mode described in the last paragraph given the match in frequency, but there are two major differences between the two processes. Firstly, in the absorption spectra the γ process appears as a clear peak. This is in contrast to the Debye mode, which typically requires the absorption to be scaled by its frequency squared in order to resolve the peak. Secondly, the γ process is without doubt temperature dependent while the Debye process is not.

An overview of the frequency dependent dynamics is shown in Fig. 1 expressed in units of dielectric loss. The dielectric loss $\varepsilon''(\omega)$ and the absorption coefficient $\alpha(\omega)$ are related by

$$\varepsilon''(\omega) = \frac{\alpha(\omega)\, n(\omega)\, c}{\omega}, \tag{1}$$

where ω is angular frequency, c is speed of light and $n(\omega)$ is the refractive index.

The spectra highlight the differences in the temperature behaviour for the dielectric relaxation processes: upon cooling of the solutions the relaxation shifts from the gigahertz region down in frequency to kilohertz frequencies (145 K) before it shifts further at low temperatures and only its high frequency wing appears in the spectrum as the peak is now at frequencies exceeding the measurement range. In contrast, the γ process is much less affected by the change in temperature and remains at terahertz frequencies throughout. However, it is clearly not independent of temperature and a subtle shift towards higher frequencies is observed upon cooling.