

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.

Keywords: Terahertz spectroscopy, Amorphous, Molecular mobility, Glass transition, Dielectric relaxation, Far-infrared, Crystallisation, Amorphous stability, Caged dynamics, Johari-Goldstein β relaxation

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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 characteristic 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 ϵ_{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 $\epsilon''(\omega)$ and the absorption coefficient $\alpha(\omega)$ are related by

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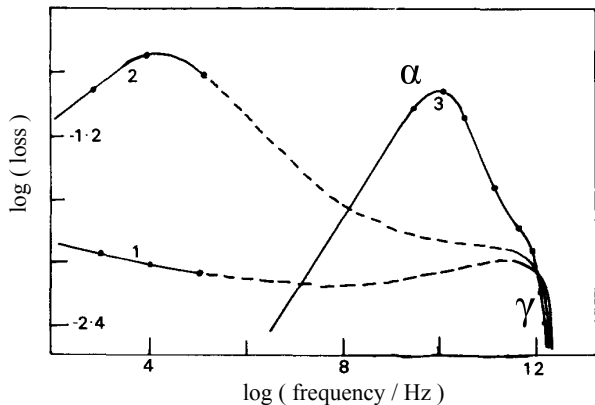


Figure 1: Dielectric loss spectrum for 10 % bromobenzene/decalin. As the liquid is cooled from 293 K the main relaxation (α) moves to lower frequencies, while the peak at terahertz frequencies (here labelled as the γ process) remains in the terahertz region. 1: 110 K (glass). 2: 145 K (ultraviscous liquid); 3: 293 K (liquid). Figure modified from [18].

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

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.

2.3. Raman and Neutron Scattering

Complementing the FTIR measurements, a range of scattering techniques, including Raman and neutron scattering, were used to probe the molecular dynamics at terahertz frequencies (for example, [20–25]). Typically the spectra reveal a single peak that develops at terahertz frequencies (or corresponding energy values of a few meV) as the sample liquid becomes supercooled or a glass. This type of spectral feature is often referred to as the boson peak.

Given the similar frequency and energy range of Poley absorption, the γ process and the Boson peak, it seems intuitive to look for a link in the molecular origin of all three processes. As Johari discusses, these features appear remarkably similar when ignoring any molecule-specific effects [16]. However, it is important to keep in mind that it is not always straightforward to compare results obtained by different experimental techniques in absolute terms as the different physical fundamental processes interrogated are excited by different forces.

For example, dielectric spectroscopy will excite dipolar moments while Raman spectroscopy is sensitive to the polarisability of the molecules. Therefore, it is not too surprising that the shape, width and centre frequency of the spectral features observed at terahertz frequencies in disordered systems by different techniques are not the same but similar [26–28]. The terahertz dynamics in (supercooled) liquids and glasses is further complicated by the fact that rotational, vibrational and relaxational movements of molecules often overlap and are difficult to separate.

3. Terahertz Molecular Dynamics in Organic Amorphous Systems

Some of the first examples of THz-TDS to study amorphous materials investigated the fundamental absorption process in inorganic glasses [29] and the glass transition and subsequent crystallisation of amorphous drugs [30]. These pioneering studies were recently followed up by a systematic analysis of a series of glass-forming liquids, which further explored in detail the different types of molecular mechanisms that contribute to the absorption of terahertz radiation and how temperature resolved terahertz measurements can be used to resolve and quantify the respective processes [31]. Based on this work on polyols it was found that three molecular absorption mechanisms govern the terahertz response in organic amorphous systems: (i) the vibrational density of states (VDOS), (ii) caged dynamics, and, (iii) dielectric relaxations (Fig. 2).

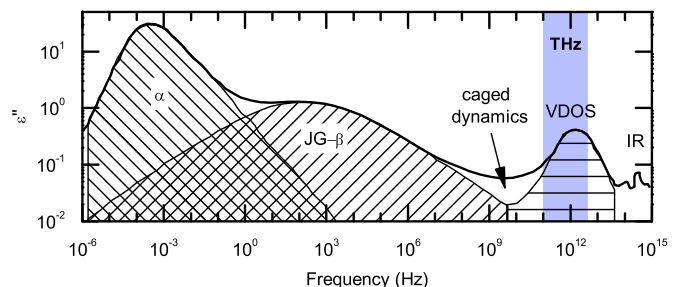


Figure 2: An overview of the dielectric response of disordered materials. α : primary relaxation, JG- β : JG secondary relaxation, caged dynamics: nearly constant loss region, VDOS: vibrational density of states peak and IR: intramolecular infrared modes. The blue shading marks the frequency window that is accessible using a typical THz-TD spectrometer. Adapted from [32].

3.1. Vibrational Density of States and Boson Peak

The principal absorption mechanism of terahertz radiation (> 0.1 THz) by amorphous solids is via coupling of the photons to the VDOS [29], sometimes also referred to as the microscopical peak. This microscopical peak is relatively broad and spans most of the terahertz range [33] (e.g. ~ 0.5 – 7 THz in the case of glycerol, see [34]). However, the microscopical peak is not necessarily a single peak and may show an underlying multi-peak fine structure [35]. Debye theory predicts a frequency-squared dependence of the VDOS which is in good agreement with the earlier far-infrared observations in inorganic glasses by Strom

[17]. The excess density of states above the Debye level is generally termed Boson peak [29, 36]. To avoid confusion, it is vital to emphasise in this context that some authors refer to the whole VDOS peak as the ‘boson peak’ [33], and further care must be taken as the term boson peak is also commonly used in the context of Raman and neutron scattering (see also Sec. 2.3). As outlined above, the boson peak, by definition, refers only to the part of the VDOS above the Debye level. The VDOS measured by terahertz spectroscopy is indiscriminate and measures overall contribution, not just the density of states in excess of the Debye level. However, it is important to note that a signature of the actual boson peak can be observed in both absorption coefficient (when plotted divided by the square of frequency) and refractive index as outlined recently [37]. As mentioned in Sec. 2.2, in earlier literature the VDOS peak was also often referred to as the γ process [18]. For clarity, we therefore will not use the term ‘boson peak’ for the remainder of this review.

3.2. Caged Dynamics

In amorphous solids, the part of the terahertz loss spectra at frequencies below the onset of the VDOS, i.e. below ~ 0.5 THz, is very close to zero, yet not actually zero. At these frequencies the so-called caged dynamics as described by Ngai’s coupling model contribute to the terahertz spectra [38]. The caged dynamics span the frequency range between the primitive relaxations (which shows remarkable similarity to the Johari-Goldstein secondary relaxation process [39]) and the VDOS. Caged dynamics refers to the fast rattling process that a molecule experiences in the cage formed by its neighbouring molecules. Sometimes this process is also called the fast relaxation, although this term is not correct in that, in reality, no distinct relaxation process can be associated with the motion because it spans a broad range of frequencies and exhibits only little frequency dependence (hence also referred to as the nearly constant loss region, NCL [38]).

Perhaps the most significant outcome of the terahertz studies of amorphous polyalcohols [31] was the observation of two separate changes in terahertz absorption with temperature: one at $T_{g\alpha} \sim T_g$ and the other at $T_{g\beta} \ll T_g$. The subscripts in T were introduced deliberately as the authors originally thought that the corresponding transition temperatures are linked to the decoupling of α - and JG- β relaxations from the VDOS [31]. However, more recently it was shown that, despite their broad nature, both relaxations are too slow to contribute to the terahertz dynamics directly. While it is correct that the temperatures $T_{g\alpha}$ and $T_{g\beta}$ do in fact correspond to the vitrification of the α - and JG- β relaxations respectively, the true origin of $T_{g\alpha}$ and $T_{g\beta}$ at terahertz frequencies is the influence of the vitrification on the caged dynamics, and in particular on the cages themselves [40]. Nonetheless, THz-TDS measurements clearly showed the existence of a secondary glass transition at $T_{g\beta}$ in small molecular glasses [31], and the publication of these results triggered the re-examination of data from other high frequency spectroscopies including neutron scattering, light scattering, Brillouin scattering, and inelastic X-ray scattering [40–42].

3.3. Primary and Secondary Dielectric Relaxations

While the Johari-Goldstein secondary relaxation and the primary relaxation are fundamentally too slow to be measured at terahertz frequencies at temperatures below T_g , it is clear that at higher temperatures $T_{\beta, \text{THz}}$ and $T_{\alpha, \text{THz}}$ the respective relaxation processes will contribute to the terahertz dynamics directly. Here one expects that $T_{\beta, \text{THz}} < T_{\alpha, \text{THz}}$, as the JG- β relaxation is faster than the primary relaxation and will therefore reach the terahertz region at lower temperatures already. Indeed, initial high-temperature terahertz data on supercooled glycerol and sorbitol suggest that this is the case [43]. The temperature difference between these two events is similar to the temperature difference between the $T_{g\beta}$ and $T_{g\alpha}$, that is, between the onset of local and global mobility in the glass. Further studies are required to assess the universality of these preliminary observations, although it should be noted that the interpretation of these results is strongly supported by positron annihilation lifetime spectroscopy (PALS) experiments at gigahertz frequencies, where a clear change is observed in signal intensity at temperatures where primary and JG- β relaxation reach the gigahertz frequency region. Given the higher frequency in the THz-TDS measurements such phenomena will be expected to be observed at slightly increased temperatures, which is in excellent agreement with the available experimental data [43].

4. Single Component Disordered Pharmaceutical Systems

4.1. Partly Disordered Systems

Terahertz spectroscopy has been used extensively for the past decade to probe low frequency phonon modes in crystalline materials in general and hydrogen bonding molecular crystals in particular [44–47]. These low frequency dynamics are very sensitive even to small structural changes, allowing terahertz spectroscopy to identify structurally very similar crystals and often even exceed the sensitivity of other spectroscopic techniques commonly used for polymorph identification such as Raman spectroscopy [13, 48–50].

Apart from the identification of crystalline polymorphs, terahertz spectroscopy is an effective tool to probe subtle disorder within the solid-state structure. An example system is the tautomeric polymorphism of irbesartan [51]. Irbesartan is known to exist in at least two different polymorphs, forms A and B. Irbesartan form B exhibits conformational disorder within the n-butyl hydrocarbon chain. Such disorder of the crystal structure may alter some of the physical properties of the material such as its solubility, physical stability or compressibility and thus can have significant impact on the quality of pharmaceutical products. Terahertz spectra revealed not only distinct features for each polymorph but also allowed for characterisation of the conformational disorder. The subsequent computational simulations of the vibrational modes in periodic structures showed that the disorder in this crystal structure arises from a competition between internal conformational strain and external cohesive binding [51].

In another study terahertz spectroscopy was shown to be highly sensitive to the location of the hydrogen atom position in

the dimers formed between the carboxylic acid groups of crystalline benzoic acid [52]. Within the context of their crystal structure environment the carboxylic acids are not identical and hence the hydrogen position introduce structural disorder, the extent of which changes with temperature. The evolving disorder in the hydrogen atom positions influences the terahertz spectrum profoundly: discrete vibrational modes break and develop into a large number of weaker features due to the broken local symmetry in the structure. The main spectral features are strongly influenced by changes in the inter-dimer interaction and, by comparing the experimental results with computational simulations, it was possible to benchmark the high sensitivity of terahertz spectroscopy to this type of disorder [52].

Succinonitrile is an orientationally disordered – yet spatially ordered – molecular plastic crystal at room temperature [53]. The orientational disorder arises from the rotation of its central carbon-carbon bond, allowing for gauche-trans isomerisation dynamics. Cooling succinonitrile below temperatures of 238 K the high-temperature rotational disorder of the plastic crystal phase is frozen out and succinonitrile forms a rigid crystal with monoclinic unit cell that exhibits two distinct phonon modes at terahertz frequencies. The authors were able to show that both modes are suppressed upon adding lithium salt (LiTFSI) to succinonitrile, hence highlighting that the presence of an ionic dopant strongly affects the long-range order of the rigid crystal structure and induces disorder [53]. In a pharmaceutical context the importance of such subtle changes in disorder of the crystal structure was demonstrated at the example of simvastatin [54]. The THz-TDS study showed clearly that the polymorphism in simvastatin is a direct result of the disorder of the ester group which can rotate quite freely in all known polymorphs of this molecule. The authors also showed that, even though none of the vibrational features in the spectra of the different simvastatin polymorphs completely disappeared and no additional features appeared (Fig. 3), it was still possible to identify easily the phase transition points between the different forms and resolve different degrees of disorder in the molecular dynamics which were in excellent agreement with previous simulations.

4.2. Small Organic Molecules

4.2.1. Local and Global Inter-Molecular Mobility

In dielectric spectroscopy the primary relaxation expresses the overall molecular mobility in the (supercooled) liquid. It provides a measure of the global mobility due to its (long-range) cooperative nature (see e.g. [55, 56]). The primary relaxation was found to play a significant role during ageing and crystallisation of supercooled liquids at temperatures above T_g ; yet it also seems to play some role at temperatures just below T_g [57]. While attempts have been made to explain even phenomena at temperatures well below T_g in relation to the primary relaxation, several studies highlight that at such low temperatures the local (short-range) inter-molecular mobility, usually expressed as the JG- β relaxation, plays a more significant role [55]. As shown in the previous section, THz-TDS is an excellent tool to determine both the onset of the local as well as global molecular mobility given its ability to measure the cage

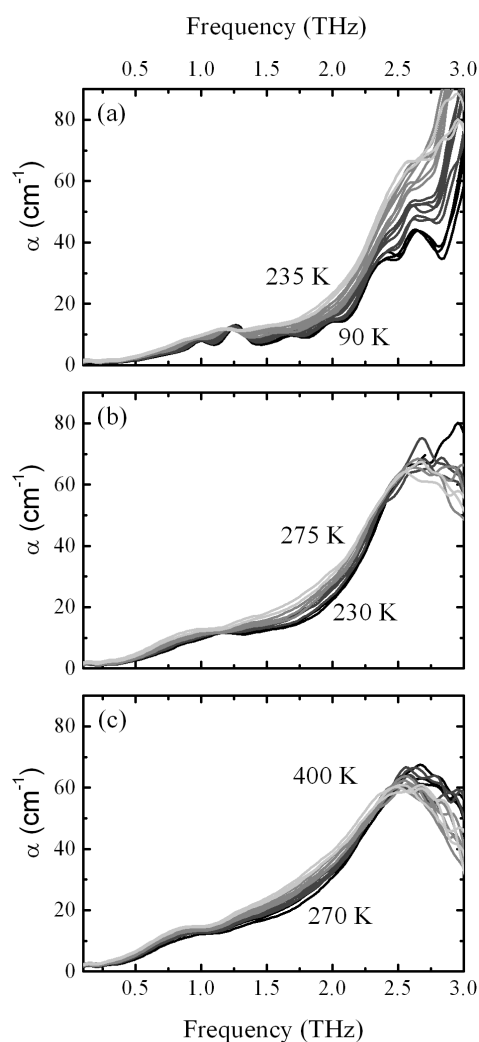


Figure 3: (a) Terahertz absorption spectra of simvastatin from 90 to 235 K, (b) terahertz absorption spectra from 230 to 275 K, (c) terahertz absorption spectra from 270 to 390 K corresponding to form I. In each plot the lowest temperatures are represented in black and highest temperatures in light grey. The temperature increment between spectra is 10 K from 80 to 210 K and 290 to 390 K, and 5 K from 210 to 290 K. Modified from [54].

dynamics that are directly coupled to the respective relaxation processes, and hence can provide further insight into the stability and crystallisation of amorphous drugs.

4.2.2. Stability of Amorphous Drugs below T_g

While the formulation of amorphous pharmaceutical solids offers a promising way to overcome solubility limitations of many drug candidate molecules, one of the major hurdles is the lack of understanding and quantitative analysis of the factors that govern the crystallisation of amorphous solids. As a consequence the long-term storage of the amorphous products poses a major risk. The recrystallisation process is complex: it involves both the formation of crystal nuclei and, following on from this, crystal growth. The kinetics of recrystallisation, which in turn describes the physical stability of amor-

phous systems, has been linked to thermodynamic [58, 59], kinetic [60, 61] and molecular driving forces [62–64]. Qualitatively it can be asserted that the difference in energy between the amorphous and crystalline state is the driving force of the crystallisation, while the molecular mobility serves as its facilitator, enabling the nuclei formation and crystal growth [65].

It is well established that the molecular mobility, and with it the risk of recrystallisation, can be reduced by storing amorphous systems at temperatures below their respective T_g as well as at low humidity [66, 67]. Traditionally, it has been assumed that a glass is completely stable below the Kauzmann temperature T_K [68], which can be roughly estimated as $T_g - 50$ K [59, 66, 69]. The assumption was that by cooling a glass to the Kauzmann temperature the primary molecular mobility, which is characteristic for liquids, is so slow that it effectively ceases to exist on the time-scales that are relevant for drug product storage. It is however becoming clearer that even at such temperatures there is commonly sufficient molecular mobility, originating from the JG- β relaxation [55, 70–72], to result in crystallisation. While the most commonly used technique to observe these relaxation processes directly is dielectric spectroscopy, experimental data from light and neutron scattering measurements shows that the molecular dynamics at time-scales of nanoseconds to picoseconds that can be resolved by these methods are equally responsive to alterations in the molecular dynamics that take place during the glass transition [73, 74] and which reflect on the overall stability of glasses [75].

Given the ability of terahertz spectroscopy to measure accurately the onset of the local mobility upon heating a sample from temperatures $T_{g\beta} \ll T_g$, it provides an excellent way to determine the risk of crystallisation qualitatively when comparing different samples, and to quantify the molecular mobility present in the material. A recent study established the correlation between the thermal gradient of terahertz absorption and stability properties [76]: the higher the thermal gradient of terahertz absorption between the $T_{g\beta}$ and $T_{g\alpha}$, the larger the contribution of the local mobility that can facilitate the crystallisation and hence the poorer the stability of the amorphous system, despite being below T_g (see Fig. 4). This result suggests that it is possible to use THz-TDS measurements as an analytical method to rank and quantify the stability properties of amorphous drug molecules. From a theoretical perspective it can be concluded that the same information can be extracted by means of neutron and light scattering. However, the comparatively wide availability, cost and ease of use of THz-TDS compared to the other techniques make the terahertz technique very attractive for such measurements.

4.2.3. Crystallisation of Amorphous Drugs Below T_g

The key role of the local mobility, or JG- β relaxation, in facilitating the crystallisation process was established experimentally in a recent study of naproxen [76]. Amorphous naproxen is very unstable and has a strong tendency to crystallise. In the study, a melt of naproxen quenched-cooled using liquid nitrogen and the resulting sample was mostly amorphous (Fig. 5). However, the lowest temperature spectrum (100 K) that was acquired immediately after quench-cooling also clearly high-

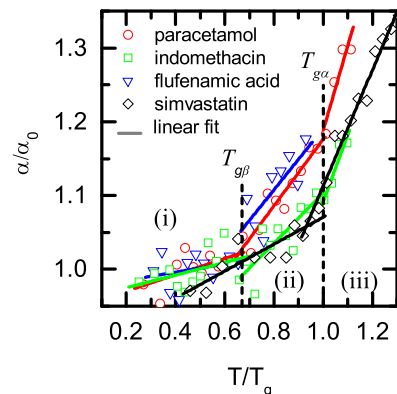


Figure 4: Absorption of amorphous paracetamol, flufenamic acid, indomethacin and simvastatin at 1.0 THz. For each sample the absorption coefficient is rescaled by its low-temperature average α_0 . The temperature is rescaled by $T_g = T_{g\alpha}$ and the solid lines represent linear fits. Paracetamol and flufenamic acid both exhibit a large increase in absorption upon heating between $T_{g\beta}$ and $T_{g\alpha}$. They are highly unstable and recrystallise within a few minutes at ambient conditions. In contrast, simvastatin shows only a small increase in terahertz absorption upon heating between $T_{g\beta}$ and $T_{g\alpha}$ and remains amorphous for over 220 days under ambient conditions. Indomethacin represents an intermediate case, staying stable for about 7 days before recrystallisation. Modified from [76].

lights the presence of a weak shoulder at around 1.2 THz. This spectral feature originates from trace crystallites that are still present in the quench-cooled sample as it was impossible to prepare a fully amorphous sample specimen using this preparative method. In contrast to the temperature dependent absorption observed for pure amorphous phases, where an increase in absorption due to the emergence of the relaxation processes occurs, the sample of amorphous naproxen that contains seed crystals steadily crystallises even at temperatures well below T_g . Nucleation has already occurred during sample preparation and crystal growth is observed with increasing temperature which is characterised by a decrease in the overall absorption losses (Fig. 5). Upon heating, a peak at 1.4 THz emerges from the shoulder. What is most interesting in the context of amorphous stability is that the results show that the crystallisation of amorphous naproxen commences at temperatures well below T_g in the presence of seed crystals.

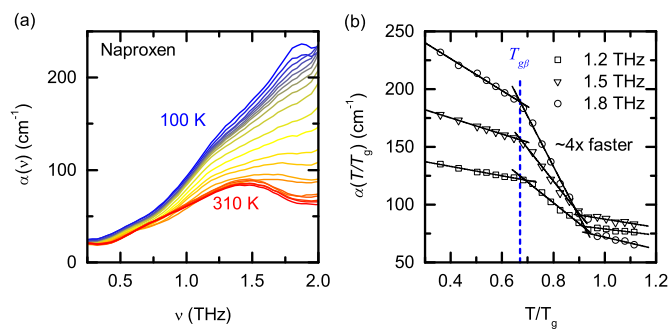


Figure 5: (a) Terahertz spectra in the thermal range 100 – 310 K of partially crystalline naproxen prepared by quench-cooling of its melt. (b) Terahertz absorption coefficient at 1.2 THz, 1.5 THz and 1.8 THz as a function of rescaled temperature T/T_g . The solid lines represent a linear fit. Adapted from [76].

When the absorption is plotted again as a function of rescaled temperature T/T_g a striking fact is revealed: at temperatures above $T_{g\beta}$ the decrease in absorption is about 3.5 times faster than below this temperature. This coincides exactly with the temperature where the JG β -relaxation enters the terahertz frequency range which, as stated above, plays a crucial role in the crystallisation of glasses below T_g . Thus, one must be very careful when evaluating the stability of a glass above $T_{g\beta}$ as this state is inherently unstable; albeit the crystallisation tendency of naproxen is extraordinarily strong and the presence of crystalline seeds almost certainly triggered a further crystallisation process even at low temperatures.

4.2.4. Crystallisation of Amorphous Drugs Above T_g

Several studies explored the changes in the terahertz spectra to investigate the crystallisation kinetics of amorphous drugs at temperatures above T_g . It was shown that terahertz spectroscopy is sufficiently sensitive to detect the glass transition, crystallisation of amorphous drugs together with any subsequent phase transitions between crystalline polymorphs upon slow heating of a free standing amorphous sample pellet of carbamazepine that was kept under a nitrogen atmosphere throughout the measurements [77]. A similar study was performed on amorphous paracetamol [78] but, in contrast to the previous study, this work was carried out by confining a small amount of amorphous paracetamol between two flat faced quartz windows and the sample was kept in a vacuum throughout. Paracetamol is known to exhibit a rich crystallisation behaviour: a fully enclosed sample crystallises from the amorphous phase upon heating above $T_g = 296$ K into its crystalline form III (~ 335 K), followed by a phase transition to form II (~ 375 K), form I (~ 405 K) and subsequent melting (~ 455 K) as shown in Fig. 6. In another study, McIntosh et al. monitored the crystallisation of amorphous lactose using terahertz spectroscopy at elevated humidity at room temperature [79]. Here sufficient molecular mobility for crystallisation is achieved by diffusion of water molecules into the crystalline phase, which results in a drop in T_g , and crystallisation commences much faster compared to the dry sample at room temperature.

Several methods can be used to extract the crystallisation kinetics from the terahertz spectra. Perhaps the most straightforward approach is to monitor the change in height or intensity of a crystalline resonance peak as crystallisation occurs [77]. McIntosh et al. used the same approach and showed that it is possible to describe the change in peak intensity with time during crystallisation by employing Avrami type kinetics [79]. In addition, they also proposed that it is possible to describe the terahertz spectra during the course of crystallisation by a linear combination of a Lorentzian function, centred at the frequency of a crystalline resonance peak in the spectrum ν_c of specified half width at half maximum γ , and a power law describing the background absorption, resulting in [79]:

$$\alpha(\nu) = \frac{A}{1 + \left(\frac{\nu - \nu_c}{\gamma}\right)^2} + B\nu^a + C \quad (2)$$

This model assumes that the crystalline resonance peak is

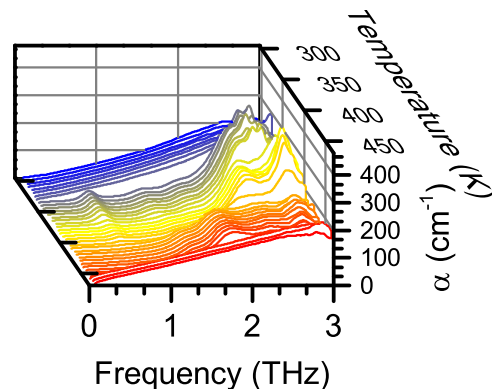


Figure 6: Absorption spectra of paracetamol at terahertz frequencies upon heating from the supercooled liquid phase over the temperature range of 295–470 K in 5 K increments. Crystallisation, subsequent phase transitions and melting can be observed by the sharp spectral discontinuities when approaching the respective transition points. Modified from [78].

well separated from any other crystalline modes, the frequency window is restricted to only include the peak at ν_c and the width of the peak does not change significantly with temperature. The changes in the fitting parameters can then be used to track the progress of the crystallisation.

A very similar method was proposed by Sibik et al. to describe the crystallisation of amorphous paracetamol [78]. The spectra were fitted with the power law only rather than including an oscillator term and the results showed that the change in the exponent is an excellent indicator for the progress of crystallisation and can also be fitted using a Avrami-Erofeev function after normalisation of the exponent value.

Both methods have in common that they use a power law to describe the overall increase in absorption with frequency in the spectral range that can be accessed using THz-TDS for amorphous materials, and which originates, as outlined above, from the VDOS. As shown by Taraskin et al. the absorption of glasses at terahertz frequencies can be described mathematically using a combination of two power laws of the form $\sim \omega^2$ and $\sim \omega^4$ [29]. The physical meaning of these equations is based in the uncorrelated (long-range disorder) and correlated (local charge neutrality) charge fluctuations, respectively. Given that the uncorrelated part typically dominates [80] a single power law with an exponent close to 2 is suitable to fit the spectra, in line with the reports by Strom previously [17].

A third method to track the crystallisation progress is to decompose the spectra directly into a linear combination of fully amorphous (α_a) and fully crystalline (α_c) spectra as [78]

$$\alpha(T, \nu) = r_a(T)\alpha_a(\nu) + r_c\alpha_c(\nu). \quad (3)$$

Here T may represent either temperature, in the case of a variable temperature experiment, or time, in the case of an isothermal experiment. The coefficients r_c and r_a directly characterise the respective crystalline and amorphous fraction which in turn can be described directly using an Avrami-Erofeev function. Again, the frequency window needs to be limited in order to satisfy the condition $r_a + r_c \approx 1$ with regards

to the scattering background in the crystalline absorption data.

4.2.5. Quantifying Crystallinity

Strachan et al. have demonstrated the ability of terahertz spectroscopy in combination with partial least-squares analysis to determine the levels of crystallinity in a mixture of amorphous and crystalline drugs as low as 1% [8]. With increasing crystallinity the intensity of the crystalline vibrational modes increases, while the absorption baseline (featureless absorption) decreases, as illustrated in Fig. 7.

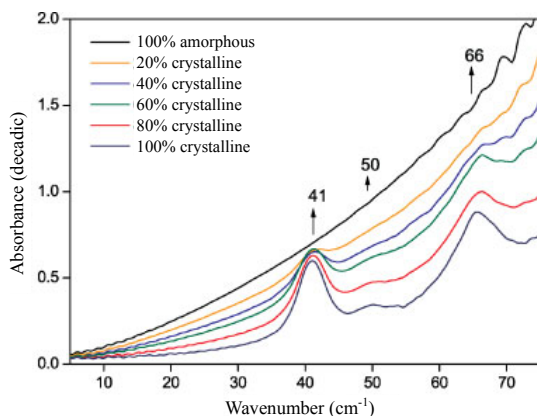


Figure 7: Terahertz spectra of binary mixtures of indomethacin amorphous and crystalline forms (20% intervals, 0 to 100% crystalline form). The arrows indicate spectral changes as the amorphous form concentration decreases and the crystalline form concentration increases. Modified from [8].

The high sensitivity of terahertz spectroscopy to detect crystallinity has also proved useful for the characterisation of amorphous drug systems prepared by different methods such as quench cooling or grinding [81], as well as spray-drying [82] and freeze-drying [83–85]. For example, amorphous samples prepared by grinding were found to contain nanoscopic crystalline particles which could be resolved in terahertz spectra but were not apparent in the XRD analysis [81]. The crystallinity detection is not restricted to glasses only, but has been demonstrated to work well also in the case of aqueous suspensions, where the water absorption is strongly affected by the presence of crystalline phase [86]. The majority of studies has demonstrated that THz-TDS is a useful technique to study the presence of small amount of crystalline phase in a largely amorphous matrix. In contrast, THz-TDS is not as sensitive or robust to detect trace amounts of amorphous phase in a largely crystalline matrix and it is also important to keep in mind that other factors, such as scattering, will have an effect of the measured absorption spectra and that this needs to be taken into account when quantifying sample crystallinity.

This point becomes clear in two studies where crystalline lactose was ball milled and samples were removed during the milling process and their crystalline content was determined [87, 88]. Here the samples were partially crystalline and like in the studies discussed above the growing amount of amorphous phase in the sample with process time will increase the background absorption of the terahertz spectra due to the collapse of the crystalline lattice modes into the VDOS. During the ball

milling process a reduction in particle size will take place concomitantly and this in turn affects the amount of scattering. In general, smaller particles scatter less and this leads to a reduction in the intensity of the spectral baseline [89]. In the study by Smith et al. this effect was not explicitly taken into account as no particle size information is provided for the milled material and potentially it is possible to increase the sensitivity of the THz-TDS technique by using this information. Overall, it should be noted that by removing the spectral baseline, either by means of baseline subtraction or any other pre-processing techniques that are commonly used in chemometrics, important information regarding the crystallinity of the sample is removed and that such baseline removal should only be performed where it can be well justified.

4.3. Large Molecular Systems

4.3.1. Intra- and Inter-Molecular Mobility

In general, large molecular systems are characterised by increasing amounts of intra-molecular flexibility, which means that they will exhibit both intra- and inter-molecular mobility. The discussion of the inter-molecular mobility by means of the processes discussed in Sec. 3, i.e. primary relaxation, JG- β secondary relaxation and caged dynamics, still apply even to such systems with higher intra-molecular flexibility.

However, in contrast to the smaller molecular systems here the intra-molecular mobility is often observed in the form of non-JG secondary relaxations [39]. Motion from such dielectric relaxation processes is generally not expected to have too much influence on the terahertz molecular dynamics, at least not universally (this is in contrast to the low energy intra-molecular vibrational motions which can significantly contribute to the VDOS but which exhibit little temperature dependence). For example, it is well known that molecules such as indomethacin do show non-JG secondary relaxation, but based on experimental results this seems to have little influence on the terahertz spectra at temperatures below $T_{g\beta}$, where the absorption coefficient stays almost constant [76] as can be seen in Fig. 4. On the other hand, in large molecular systems with significant intra-molecular flexibility, such as proteins or long polymer chains, the increase in absorption with temperature (due to the increase in NCL) becomes almost precisely quadratic, as demonstrated in Fig. 8. Such a quadratic increase in the losses at GHz-THz frequencies with temperature was already reported in the 1960s for amorphous polymers [90]. At the time it was suggested that the quadratic increase in absorption with temperature could be explained by a multi-phonon absorption mechanism [91]. This mechanism is difficult to accept in this case, given the low statistical likelihood of such complicated process occurring at low temperatures. There is, however, a different, perhaps more intuitive, way to understand the experimental data: by considering the change in absorption as a direct result of the interplay between the intra- and inter-molecular dynamics in very large molecular systems, which can be described mathematically by means of a simple convolution between these [92]. From a generalised dynamics point of view the *intra-molecular flexibility* in itself will not contribute signifi-

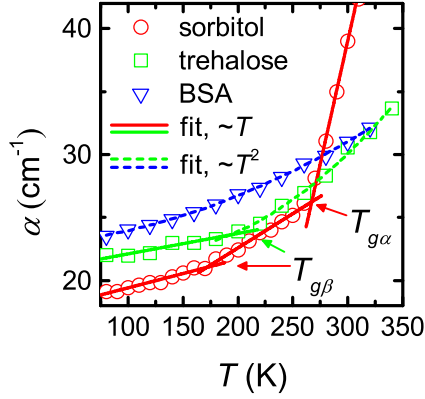


Figure 8: Terahertz absorption of amorphous sorbitol ($T_g \approx 268$ K), trehalose ($T_g \approx 385$ K) and BSA between 80–340 K at 0.8 THz. The solid lines represent a linear fit, while the dashed lines represent a quadratic fit with no linear part [92]. Modified from [93] and [94].

icantly to the thermal change in the losses at terahertz frequencies that originate from the NCL, given that the intra-molecular motions are more or less unrestricted at all temperatures (for simplicity we do not consider the cases where temperature results in geometrical restriction of the intra-molecular motion). This means that $\varepsilon''_{\text{NCL, intra}}(T) \sim \text{const.}(T) = c$. As outlined previously, the *inter-molecular flexibility* on its own results in a linear change of the amplitude of NCL with temperature [78], and hence $\varepsilon''_{\text{NCL, inter}}(T) \sim T$. This inter-molecular dynamics remains active in large molecules similar to the case described for small molecules, yet it is strongly mixed with the complex internal vibrational motions that can take place additionally in the much more flexible large molecules. Thus, when the intra- and inter-molecular molecular dynamics interfere, the overall change of NCL amplitude can be treated as a convolution between the intra- and inter-molecular mobility, i.e. $\varepsilon''_{\text{NCL}}(T) = \varepsilon''_{\text{NCL, intra}}(T) * \varepsilon''_{\text{NCL, inter}}(T) \sim \int (cT) dT \sim T^2$ [92].

The validity of this model can be illustrated by the data shown in Fig. 8. For a small molecule, such as sorbitol (molecular weight 182 Da), the intra- and inter-molecular mobility are not expected to interfere at any temperature, resulting in three linear ranges in temperature dependance of terahertz absorption, similar to the behaviour of small molecular drugs discussed previously (Fig. 4, note that for sorbitol $T_{g\beta} = 178$ K and $T_{g\alpha} = T_g = 268$ K [78]). In the case of the still small, yet more flexible compared to other sugars such as dextran, sugar trehalose (molecular weight 342 Da), the trend is linear at the lowest temperatures but becomes closer to quadratic at higher temperatures (still below T_g). The onset of the quadratic dependance can be associated with the onset of the inter-molecular mobility above $T_{g\beta}$ and some coupling between the intra- and inter-molecular mobility. Lastly, for large flexible molecular system such as bovine serum albumine (BSA, molecular weight 66500 Da) the overall temperature dependancy is well described by a quadratic behaviour over the entire temperature range of 100 – 320 K, highlighting strong coupling between intra- and inter-molecular mobility in such molecules [92].

4.3.2. Polymers

Wietzke et al. demonstrated the applicability of THz-TDS to study the glass transition in polymers [95–98], a phenomenon that was explained in this work by the concept of free volume at the molecular level in polymers. Free volume is defined as the temperature-dependent space in a polymer sample that is not occupied by the macromolecular chains due to imperfect packing inside the amorphous domains [95]. Upon cooling the free volume decreases as the material contracts. At a critical temperature, which is referred to as the glass transition temperature T_g , the remaining space is no longer sufficient for segmental motions to occur along the polymer chain axis.

The authors argued that a changing free volume in the polymer sample is reflected in its refractive index n and the temperature dependence of the refractive index can be used to measure the T_g . An example is shown in Fig. 9 for the case of semi-crystalline poly(oxymethylene) [95]. For temperatures below T_g the sensitivity of n to changes in temperature is significantly lower, resulting in the change of the thermal gradient $\partial n/\partial T$ at $T = T_g$. A similar approach has been applied to a range of semi-crystalline polymers [98].

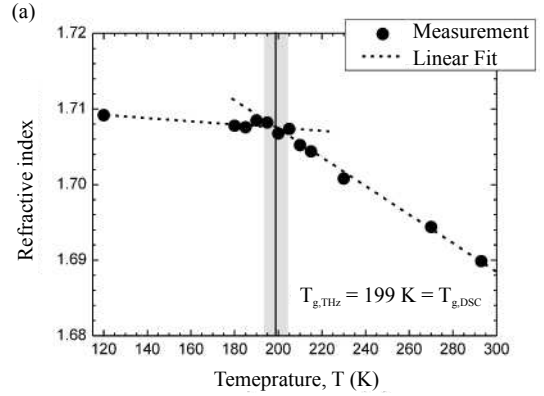


Figure 9: The temperature dependence of the terahertz refractive index reveals a glass transition of poly(oxymethylene) at $T_{g, \text{THz}} = 199$ K at the intersection of two linear fits. For comparison, the glass transition temperature interval, obtained from DSC measurements, is highlighted by the grey area. Modified from [95].

In the case of partially crystalline polymers the glass transition is a feature of the amorphous domains only and it was shown that in cases of highly crystalline polymers terahertz spectroscopy can surpass the sensitivity of standard characterisation techniques such as differential scanning calorimetry (DSC): in high-density polyethylene DSC does not observe a clear T_g . Here the glass transition region can also be identified from the shift of the crystalline lattice modes [96].

4.3.3. Proteins

In proteins the topic of the so-called dynamical transition temperature, $T_d \approx 200 - 220$ K for most proteins, has attracted considerable interest. The dynamical transition is regarded as the temperature where the additional degrees of freedom in the atomic mean square displacement over the molecule become available. This phenomenon was initially studied in frozen solutions of proteins using THz-TDS (Fig. 10) and the effect was

explained in terms of protein side chain motions that become thermally activated at $T > T_d$ and which extend to subpicosecond timescales and hence can be observed at terahertz frequencies [99]. It was further observed that the dynamical transition is independent of the presence of a secondary or tertiary structure in peptides and proteins [100].

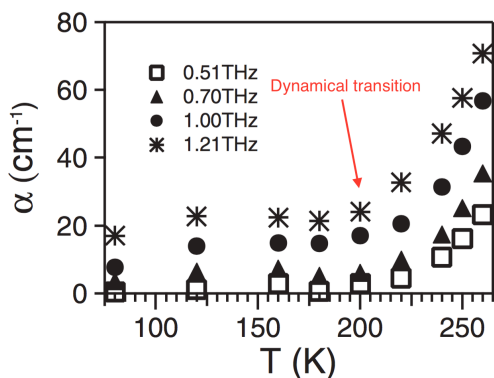


Figure 10: Terahertz absorption for random coil poly lysine from 80 – 270 K. Modified from [100].

In all these discussions it was assumed that water molecules that are in direct contact with the protein must play a key role in the change in flexibility associated with the dynamical transition. More recent studies from the same group using powder samples of myoglobin that were carefully equilibrated to different water content highlighted that this effect alone cannot explain the dynamical transition but that the vibrational response of the protein itself appears to play a significant role [101].

In light of the discussion above regarding the role of the JG- β relaxation and its link via the cage dynamics to terahertz frequencies it would appear worthwhile to further investigate the potential role this process might play in the context of the dynamical transition.

5. Multi Component Disordered Pharmaceutical Systems

While the understanding of the behaviour of single-component amorphous systems is the first and necessary step to systematically advance the field, from a practical point of view it is inevitable to expand such investigations towards multi-component systems. In order to achieve marketable pharmaceutical formulations the properties of a single-component amorphous system cannot be sufficiently adjusted to achieve all design criteria for a formulation, and hence more complex pharmaceutical and biopharmaceutical formulations are required that include the interaction with excipients. Two very relevant examples for such formulations are (i) polymer-drug dispersions and (ii) protein-sugar mixtures. To our knowledge, there has been no systematic study of the properties of polymer-drug dispersions using terahertz spectroscopy to date.

A recent study examined the properties of freeze-dried protein-sugar mixtures, examining the effects of trehalose, inulin and dextran on the stabilisation of BSA [94]. the terahertz

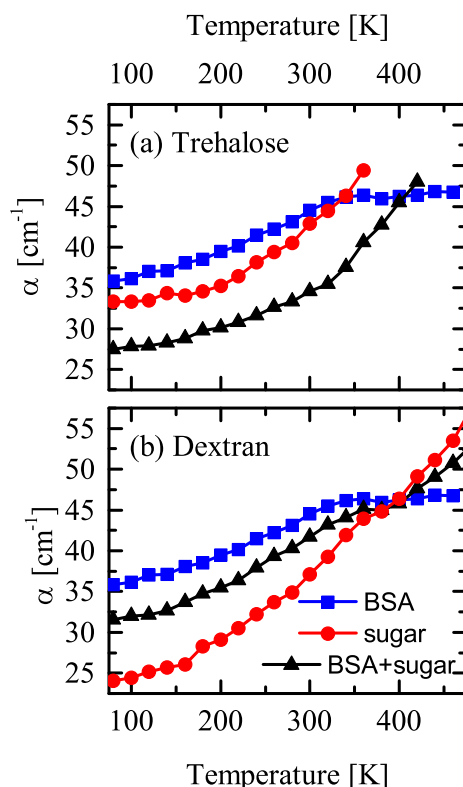


Figure 11: Terahertz absorption of (a) BSA-trehalose mixture and its components, and (b) BSA-dextran mixture and its components, at 1 THz. The molecular weight of dextran is 70 kDa. After [94].

spectroscopy data confirmed that the main factor influencing the stability of BSA in the freeze-dried sample is the intermolecular bonding between the protein and sugar. The information on the bonding between protein and sugar can again be inferred from the temperature dependance of terahertz absorption: when a significant amount of bonding takes place between the protein and sugar molecules, such as in the case of BSA and trehalose, the absorption coefficient of the mixture is not just the simple sum of its constituent components (see Fig. 11 a). On the other hand, when only little inter-molecular interaction takes place between the protein and sugar molecules, the mixture behaves like a phase-separated physical mixture and the observed absorption coefficient is close to a linear combination of the components (see Fig. 11 b) [94].

It can be expected that a similar methodology can be applied in the case of polymer-drug systems, and there is a possibility of terahertz spectroscopy being able to determine the maximum drug loading, above which partial phase-separation of the drug component might occur, with the associated risk of crystallisation. This remains a topic for future investigation.

Conclusions

The recent developments in THz-TDS have made it possible to access molecular dynamics at terahertz frequencies experimentally, which offers fascinating, unexplored, opportunities

for the characterisation of amorphous pharmaceutical materials. By investigating the temperature-dependent behaviour of materials of interest it is possible to measure the fast molecular mobility that results in structural changes in these systems and which, in turn, play a critical role for the stability of an amorphous material against crystallisation. Building on previous work based on dielectric spectroscopy experiments, far-infrared spectroscopy and scattering techniques, such as neutron scattering, there is a significant amount of data already available to establish firmly the importance of terahertz dynamics in this context. A solid theoretical framework has been established over the past fifty years to aid interpretation and explain the underlying physics of the experimental observations. However, thus far we have only scratched at the surface of what it is possible to achieve by developing a sound understanding of the terahertz dynamics in the context of pharmaceutical drugs and, more importantly, pharmaceutical formulations. It is our strong belief that the complex interplay between drug molecules and excipients¹; the implications on the energetic state of materials due to the processing routes and conditions in secondary manufacturing, and the impact of storage conditions will provide a fertile field of research for decades to come and THz-TDS will have an important role to play in this process.

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¹By the inter-molecular interactions between drug and excipient molecules as well as the change of the inter-molecular interactions of the respective individual molecular phases as a result of the competing interactions.

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