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Predicting Crystallization of Amorphous Drugs with Terahertz Spectroscopy

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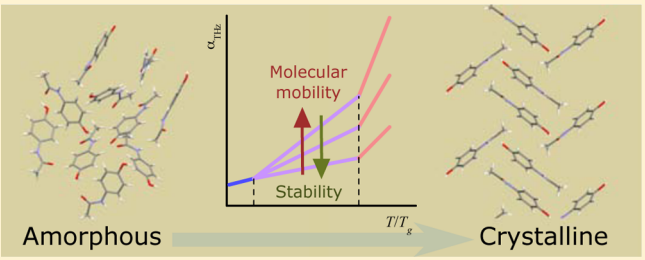
Supporting Information

ABSTRACT: There is a controversy about the extent to which the primary and secondary dielectric relaxations influence the crystallization of amorphous organic compounds below the glass transition temperature. Recent studies also point to the importance of fast molecular dynamics on picosecond-to-nanosecond time scales with respect to the glass stability. In the present study we provide terahertz spectroscopy evidence on the crystallization of amorphous naproxen well below its glass transition temperature and confirm the direct role of Johari−Goldstein (JG) secondary relaxation as a facilitator of the crystallization. We determine the onset temperature T_β above which the JG relaxation contributes to the fast molecular dynamics and analytically quantify the level of this contribution. We then show there is a strong correlation between the increase in the fast molecular dynamics and onset of crystallization in several chosen amorphous drugs. We believe that this technique has immediate applications to quantify the stability of amorphous drug materials.



KEYWORDS: *terahertz spectroscopy, amorphous, glass, stability, crystallization*

INTRODUCTION

Amorphous solids are high energy materials compared to their crystalline counterparts and characterized by the absence of a long-range three-dimensional molecular order.[1] The molecules within an amorphous material are thought to reflect the disorder in structure found in the liquid state but with rheological properties of a solid.[2] The most pronounced feature of an amorphous material is its glass transition, where an abrupt change in molecular mobility occurs.[3] Below the glass transition temperature (T_g), the molecules are in the glassy state and kinetically frozen in, characterized by low molecular mobility. Because of the high internal energy, amorphous solids generally have a higher kinetic solubility and dissolution rate.[1,4] This can be exploited for applications such as in the pharmaceutical field to increase bioavailability of poorly soluble drugs when administered orally in the form of tablets or capsules. However, from a thermodynamic point of view, these systems are unstable and experience an intrinsic drive to convert to a lower energy and stable crystalline form over time. In order to be able to exploit the properties of the amorphous form practically one needs to ensure physical stability at least for the duration of the shelf life of e.g. pharmaceutical formulations.

The process of recrystallization is a complex phenomenon of crystal nuclei formation and crystal growth. The recrystallization kinetics, and thus the physical stability of amorphous systems, has been discussed widely in the literature and was related to thermodynamic,[5,6] kinetic,[7,8] and molecular driving forces.[9−11] In order to minimize the risk of recrystallization, amorphous systems should be stored at temperatures far below T_g and at low humidity to reduce molecular mobility.[1,4] Often, it is assumed the glass is completely stable below temperatures of T_g − 20 K or T_g − 50 K, where the primary molecular mobility present in liquids no longer exists on the relevant time scales.

It is however becoming clearer that even at low temperatures there is molecular mobility that gives rise to an instability of the amorphous system, originating from the Johari−Goldstein (JG) secondary relaxation.[12−15] While this is usually best observed by dielectric spectroscopy, experimental evidence from neutron and light scattering shows that nanosecond-to-picosecond molecular dynamics measured by these techniques are also extremely sensitive to any changes in the molecular dynamics during the glass transition[16,17] and reflect on the overall stability of glassy systems.[18]

A recent study showed that terahertz spectroscopy is very sensitive to the changes in the picosecond molecular dynamics both above and below T_g.[19] It was shown that the decrease in global mobility at T_g, represented by the primary dielectric relaxation, has a clearly measurable effect on the temperature behavior of terahertz absorption. The study also found that in the case of polyalcohols, at $T_\beta \approx 0.67\ T_g$, there is another

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significant change in the picosecond molecular mobility that is strongly linked to the diminishing JG secondary relaxation.

In this work we show that the onset of molecular mobility at T_β directly facilitates the crystallization of an amorphous system deeply below its T_g and that there is a strong correlation between this type of molecular mobility and the stability of amorphous molecular systems. Hence, we outline the possibility to use terahertz spectroscopy for stability testing of amorphous systems, such as amorphous drugs, in order to prevent their crystallization over the shelf life of a final product.

MATERIALS AND METHODS

Materials. Paracetamol, indomethacin, and flufenamic acid were obtained from Sigma-Aldrich (St. Louis, MA, USA). Naproxen was purchased from Divis Laboratories Ltd. (Florham Park, NJ, USA). Simvastatin was obtained from Dalian Melian Biotech Co. (Dalian, China). All substances were of reagent grade (see Figure 1).

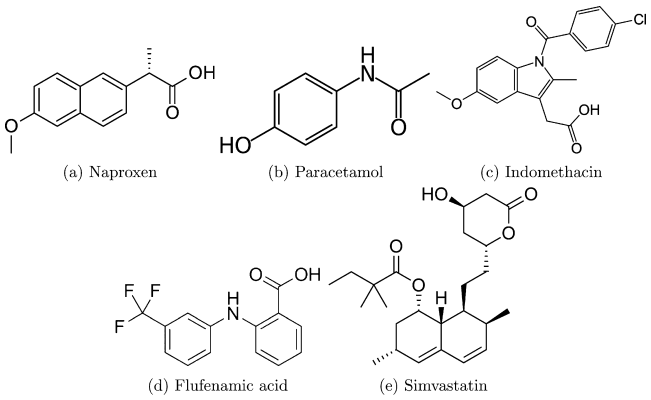

Figure 1. Molecular structures of samples used in the study.

Preparation of Amorphous Samples. The pure amorphous drugs were prepared freshly prior to the terahertz measurements by melting the crystalline powder at approximately 450 K followed by fast cooling of the melt to room temperature and subsequent slow cooling to 80 K. Because of its fast recrystallization at room temperature, crystalline naproxen was molten in situ within the sample holder and directly immersed into liquid nitrogen before the measurements.

Temperature Controlled Terahertz Spectroscopy (THz-TDS). The terahertz absorption spectra were obtained using THz-TDS as described previously.[20] Spectra were acquired in the frequency range of 0.2−2.0 THz and over a temperature range of 80−320 K. The samples were loaded between two z-cut quartz windows of 13 mm diameter separated by a PTFE spacer of 190 μm thickness. The pure naproxen sample was prepared between two PTFE windows to avoid shattering the windows during quench-cooling. The spectra were measured during heating of the sample from 80 K with 10 K steps. The estimated accuracy in temperature control is 1 K. Terahertz frequency data were extracted from the time-domain data in a fashion described elsewhere.[21]

X-ray Powder Diffraction (XRPD). XRPD was performed using a PANalytical X-Pert PRO X-ray Diffractometer (Almelo, The Netherlands) with Cu Kα radiation (λ = 1.54187 Å). The acceleration voltage and current were 40 kV and 30 mA. Samples were analyzed in reflection mode between 5° and 35° 2θ applying a scan speed of 0.1285° 2θ/s and a step size of 0.0084° 2θ.

Differential Scanning Calorimetry (DSC). Glass transition temperature (T_g, midpoint) determination was performed using a TA Discovery DSC (TA-Instruments-Waters LLC, New Castle, DE, USA) attached with a TA Instruments Quench Cooling Accessory (Q Series). Approximately 3−5 mg of amorphous sample were crimped into a Tzero aluminum pan with lid. Measurements at a scanning rate of 10 K/min were carried out from 150 to 10 K above the melting point of the respective compound.

Physical Stability Studies. The stability of amorphous drugs represents the onset of crystallization in amorphous samples. The onset of crystallization was determined as the time when the first crystalline reflections appeared in the XRPD diffractograms. The stability was determined for samples stored under dry storage conditions (phosphorus pentoxide) in desiccators at 277 and 298 K. The samples were exposed to room conditions during the measurement. The sensitivity of XRPD is approximately 1% of crystalline amount in amorphous material.[22]

The time resolution of the stability check procedure was as follows. The unstable samples naproxen, paracetamol, and flufenamic acid recrystallized within 1 day; therefore, they were recorded directly after preparation and the day after. Note that paracetamol and flufenamic acid recrystallized very fast at room temperature, so the observation of recrystallization was done visually by checking the samples in the optically transparent desiccator, since removing samples from the desiccator for XRPD analysis would initiate recrystallization. The visual check is straightforward as the amorphous form is a transparent glass, but when it starts recrystallizing it becomes white and cloudy. The other samples were tested roughly every week, with increasing time intervals after week 4.

RESULTS

Crystallization of Amorphous Naproxen below T_g. Terahertz spectroscopy is a very sensitive technique to monitor crystal formation in the (supercooled) liquid state above T_g.[23−25] This analysis can be extended to samples that crystallize below T_g. An excellent example of such a material is naproxen, which has an extraordinarily strong tendency to crystallize even at temperatures below its T_g = 279 K. Amorphous naproxen is stable for only about 1 min at a temperature of 273 K (T_g −5 K), and very rapid cooling rates are necessary to obtain samples of fully amorphous naproxen.[26]

The terahertz spectra of naproxen are shown in Figure 2. In general, fully amorphous systems exhibit a power-law frequency dependence of terahertz absorption due to the coupling of the terahertz radiation to the vibrational density of states (VDOS), and no distinct narrow spectral peaks, as commonly observed in the crystalline state, are expected at frequencies below 3 THz for organic materials.[19,27−29] Upon heating an amorphous sample the terahertz absorption is expected to increase as a result of an increasing molecular mobility.[19]

The spectra of naproxen at 100 K reveal a broad peak centered at around 1.25 THz, which becomes sharper upon further heating of the sample and its subsequent crystallization. This means that a small amount of crystalline seeds was already present in the sample following the preparation by quench-cooling. A pure amorphous sample could not however be obtained even after multiple attempts of fast quench-cooling by submerging the sample cell directly into liquid nitrogen.

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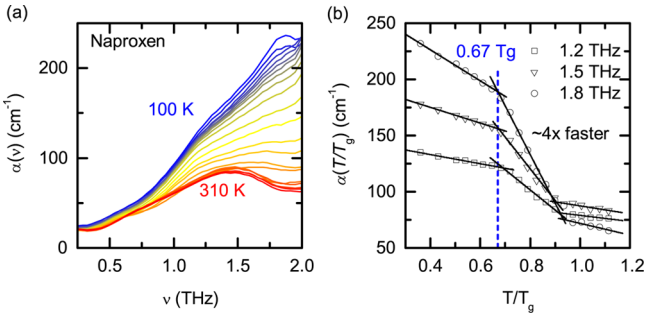

Figure 2. (a) Terahertz absorption spectra of quench-cooled naproxen in the thermal range 100−310 K. (b) Terahertz absorption coefficient at 1.2 THz, 1.5 THz, and 1.8 THz as a function of rescaled temperature T/T_g. The solid lines represent a linear fit. [Given the difficulty in the sample preparation the absolute values of the absorption coefficient are likely to be affected to some extent by scattering of terahertz radiation on the crystalline seeds and possibly lack of perfect plane-parallelism of the sample. The impact of these discrepancies on the relative change of absorption with temperature is however insignificant.]

The spectra in Figure 2 clearly reveal that the naproxen sample crystallized continuously upon heating and was fully crystalline at around 270 K, close to its T_g. A visual check confirmed that the sample of naproxen was fully crystalline at the end of the experiment. The presence of crystalline seeds in the sample most likely acted as nucleation centers for the subsequent crystallization. The absorption changes with temperature in a linear fashion (Figure 2b). The linear analysis in Table 1 shows that the decrease in absorption becomes

Table 1. Linear Coefficient c of Change in Absorption with Temperature Determined from the Linear Fit $\alpha(T/T_g) = a + cT/T_g$ of Naproxen in the Temperature Region below $0.67T_g$ (c_1) and between $0.67-1.0T_g$ (c_2) at 1.2 THz, 1.5 THz, and 1.8 THz[a]

frequency (THz)	c_1 (cm^{-1})	c_2 (cm^{-1})	c_2/c_1	T_β/T_g	T_β (K)
1.2	−41	−179	4.4	0.69 ± 0.08	192 ± 22
1.5	−79	−281	3.6	0.70 ± 0.08	196 ± 21
1.8	−138	−432	3.1	0.67 ± 0.06	187 ± 17

[a] T_β designates the crossover temperature between the two thermal regions.

about 4 times larger when the temperature exceeds 190 K, ≈ 0.67, T_g. It has been previously shown that in the case of amorphous organic systems there is a temperature $T_\beta < T_g$ above which the molecular mobility becomes enhanced despite the system being still deeply in its glassy state. This onset of mobility is linked to the JG relaxation having an influence on the fast caged dynamics of molecules, as explained further in the section 'Origin of T_β'. For example, in the case of amorphous polyalcohols it was shown that $T_\beta \approx 0.67\ T_g$.[19] This temperature matches extremely well with the observed enhancement of naproxen crystallization in Figure 2 with our previous observation of T_β, i.e. the onset of the fast molecular mobility due to the JG relaxation.[19] The results on naproxen therefore directly demonstrate the connection between T_β, fast molecular dynamics and ability of amorphous material to crystallize.

Correlation of Terahertz Spectra with the Stability of Amorphous Drugs. Similarly to the previous study of polyalcohols,[19] the amorphous drugs also exhibit the same behavior of $T_\beta \approx 0.67\ T_g$ as can be seen from the spectra of amorphous paracetamol and indomethacin in Figure 3. While

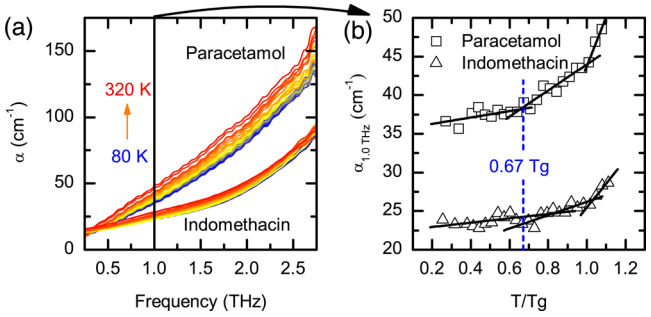

Figure 3. (a) Terahertz absorption spectra of amorphous paracetamol and indomethacin in the thermal range 100−320 K. (b) Terahertz absorption coefficient at 1.0 THz as a function of rescaled temperature T/T_g. The solid lines represent a linear fit.

the absolute level of terahertz absorption of polyalcohols in the previous study was very similar, this is no longer true for the drugs in this study. Therefore, in order to be able to compare the increase in the terahertz absorption due to the onset of molecular mobility at temperatures above T_β it is necessary to rescale the temperature by T_g and also to find a comparable metric to normalize the absorption coefficient. We rescale the absorption coefficient by the average of its values below 0.67 T_g at a frequency of 1 THz. This particular frequency was chosen as our terahertz system provides the highest sensitivity around this frequency.

The rescaled absorption at 1 THz for amorphous paracetamol, indomethacin, flufenamic acid, and simvastatin are shown in Figure 4. Generally, these results exhibit three

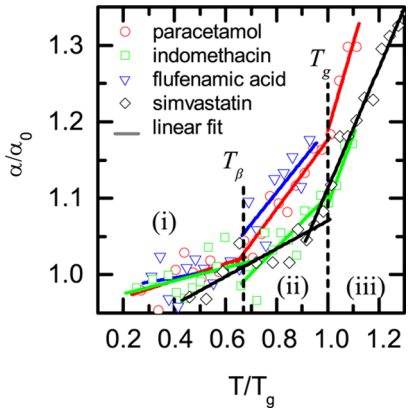

Figure 4. Terahertz absorption spectra of amorphous paracetamol, flufenamic acid, indomethacin, and simvastatin at 1.0 THz. The absorption coefficient is rescaled by the low-temperature average α_0; the temperature is rescaled by T_g. The solid lines represent a linear fit.

different temperature regimes, similarly to what was previously observed in case of polyols:[19] (i) very weakly temperature-dependent absorption at the lowest temperatures, (ii) intermediate temperature dependent absorption at higher temperatures yet still below T_g, and (iii) relatively strongly dependent terahertz absorption above T_g. Data in the regions (i), (ii), and (iii) of these regions were fitted using a linear function $\alpha/\alpha_0(T/T_g) = A + BT/T_g$, separately for all three

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thermal regions, except for simvastatin where such an attempt was hampered by barely distinguishable regions (i) and (ii). Simvastatin showed a significant increase in the terahertz absorption from 285 K onward despite the fact that its T_g = 303 K as determined by DSC. It is not clear what the molecular origin of this discrepancy is between the thermal behavior and the molecular relaxations. We believe that this is likely owing to the intramolecular flexibility of the simvastatin molecule and its ability to form partly disordered conformations via rotations of the ester tail with low energy barriers between these.[30] For the linear fitting we therefore decided to use T_g = 285 K, as it reflects on the actual molecular dynamics and provides an upper estimate of the absorption thermal coefficient B_2. The temperature T_β corresponds to the transition point between regions (i) and (ii) and has been determined by extrapolating the linear fits of data in the regions (i) and (ii), respectively.

The outcomes of the linear fitting are shown in Table 2, where we show the crossover temperature T_β between regions (i) and (ii) as determined from adjacent linear fits, together with the linear thermal absorption coefficient B_2 obtained for temperature region (ii) as well as the stability data. The stability of the amorphous drugs was determined as an onset of the first detectable traces of the crystalline phase in the XRPD diffractograms. One may immediately notice a correlation between the stability results and absorption thermal coefficient B_2.

Table 2. Stability t_{stable} of Studied Amorphous Drugs Expressed As Time before Any Crystallization Was Detected at 277 and 298 K, Glass-Transition Temperature T_g Determined by DSC, Together with the Linear-Fit Analysis of Absorption Losses, $\alpha/\alpha_0(T/T_g) = A + BT/T_g$, as Shown in Figure 4[a]

sample	t_{stable} at 277 K (day)	t_{stable} at 298 K (day)	T_g (K)	T_β (K)	T_β/T_g	B_2
flufenamic acid	4	1	285	160	0.55	0.42 ± 0.15
paracetamol	45	1	297	194	0.65	0.45 ± 0.05
indomethacin	136	7	318	243	0.76	0.34 ± 0.09
simvastatin	>84	>220	303			0.18 ± 0.03

[a] B_2 is the linear coefficient obtained from fits in the temperature region between T_β and T_g.

DISCUSSION

Origin of T_β. While the change in the terahertz absorption at T_g and T_β is clearly linked to the primary and JG dielectric relaxations respectively as shown previously,[19] it is important to further clarify the exact mechanism. Despite their broad frequency nature, the primary and JG relaxation processes are generally too slow to extend to the terahertz frequency range at temperatures of T_g and below. However, their influence extends to the terahertz frequencies through the caged dynamics losses.[17,31] The caged dynamics result in nearly constant type of dielectric losses that cover the range between the fastest secondary relaxation and the lowest structural vibrations from the VDOS in amorphous materials. This part of the dynamics contains information on the manner in which a disordered system experiences the transition from vibrational to relaxational dynamics.[32]

It was shown previously that while the caged dynamics themselves are observed in the gigahertz frequencies region, the glass transition leads to a change in the caged dynamics, likely through the direct physical effect on the cages themselves.[16] The change of terahertz absorption with temperature at T_g (Figure 4) can therefore be explained as an effect of primary relaxation on the caged dynamics. Similar arguments can be used to explain the changes at T_β in terms of an effect of the JG relaxation on the caged dynamics. This argumentation is further supported by the fact that there is a direct link between the JG secondary relaxation time and the amplitude of the losses induced by the caged dynamics.[33] There is good evidence of JG-β relaxation present in paracetamol below T_g based on previous dielectric studies.[34] In the case of indomethacin the JG-β relaxation was also clearly observed, although only at elevated pressure.[35] Both results thus further support the relevance of the JG relaxation for the stability of amorphous solids below T_g. Unfortunately, to our knowledge there are no reported data on secondary dielectric relaxations for flufenamic acid and simvastatin.

It should also be kept in mind that due to its vibrational (librational) origin, the broad VDOS peak is expected to shift slightly to higher frequencies upon cooling a glass, resulting effectively in loss of terahertz absorption at frequencies below the maximum of the VDOS. This shift originates from the intermolecular hydrogen bonding getting stronger upon cooling. Given that we cannot resolve the full VDOS peak with our current experimental technique, it is not possible to perform an accurate analysis of this effect. It is however apparent that lowering the relaxational contribution to the terahertz absorption and shifting the vibrational contribution to higher frequencies will constructively result in lower terahertz absorption, enhancing the sensitivity of THz-TDS toward the overall effect. The task of differentiating between these effects remains to be addressed in future studies as it requires a terahertz spectroscopy system that allows one to measure dielectric losses accurately up to at least 5 THz in order to cover most of the VDOS peak.

Role of Fragility on Glass Stability. There is an ongoing dispute on the role of fragility on glass stability.[15,36] Reported values for fragility of paracetamol from various studies are m = 86.7[37] and m = 67.7,[36] and m = 64[38] and m = 60.2[36] for indomethacin. However, the fragility of simvastatin is m = 73,[36] and the relationship between the observed increase in terahertz absorption above T_β and fragility, as well as stability and fragility, does not hold. A further argument against the link of fragility to sub-T_g terahertz losses originates from the fact that glycerol has a fragility of around m = 57, close to indomethacin, yet no significant changes in the terahertz losses were observed below its T_g.[19]

The lack of relation between the fragility and glass stability has been already highlighted in previous work.[36] The present study offers further insight into this topic, as it confirms that it is the JG relaxation that plays a dominant role in the glass stability below T_g. In contrast it is important to highlight that the fragility is an expression of the diminishing molecular kinetics that are related to the primary relaxation, which however plays no role around T_β.

Role of Intermolecular Bonding on Glass Stability. Commonly the primary and secondary relaxations are considered to be the source of the molecular mobility while in reality they are only a consequence of it. The molecular mobility, that allows for relaxation of glass and the occurrence of crystallization, originates from the chemical bonding between the molecules. It has been shown, especially in multicomponent

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systems, that molecular interactions (e.g., hydrogen bonding) play a crucial role in the stabilization of the amorphous form.[39,40] In the coamorphous systems naproxen-cimetidine and indomethacin-naproxen for example, it was found that the low-range molecular order found between the molecules in the systems, i.e. maximum amount of intermolecular interactions, resulted in physically more stable systems regardless of the T_g.[26,39]

Several studies on thermal changes in chemical bonding of glass-formers around T_g, focusing on different functional groups, were performed previously with IR spectroscopy.[41,42] However, these measurements did not specifically aim to resolve any changes in the corresponding vibrational modes around $T_\beta \approx 0.67\ T_g$ and only report data at higher temperatures. Careful low-temperature FTIR analysis of sorbitol however clearly shows a significant change in the −OH stretch mode observed around 3300−3500 cm^{-1} (approximately 100 THz) in both T_g and 0.67 T_g thermal regions and confirms the presence of changes in the intermolecular hydrogen bonding at these temperatures.[43]

We attempted to perform a similar FTIR analysis on paracetamol, where the signature of T_β is the strongest. There is some quantitative change in the spectra with temperature, in particular around T_g, but in paracetamol the −OH stretch region is strongly broadened and overlaps with the −CH stretch region and others (data not shown) and hence the process cannot be resolved. This is a common scenario for many larger molecular systems that makes it impossible to conclusively resolve the underlying changes in intermolecular hydrogen bonding based on FTIR (or Raman at mid infrared frequencies) data.

While the samples studied in this work form intermolecular hydrogen bonds, there is also a significant proportion of weak van der Waals dipolar intermolecular interaction present. Given the clear observation of T_β by THz-TDS in all cases it is however very likely that T_β is originating from the disorder in the samples rather than a specific type of intermolecular bonding. This question will need to be further addressed in future studies.

Role of T_β for the Stability of Amorphous Drugs. The results presented in this paper point toward two very important conclusions:

First, the terahertz absorption increase between T_β and T_g correlates with the stability of amorphous drug molecules. We show that the fast (GHz-THz) molecular processes are governing the stability and crystallization of the amorphous materials below T_g. An analogous conclusion has been previously reached in terms of protein stability in glassy matrices by Cicerone et al. as measured by neutron scattering.[18] THz-TDS could therefore offer a convenient analytical method to assess amorphous drug or lyophilized protein stability without the necessity to perform midterm or long-term storage stability experiments. The robustness of terahertz spectroscopy is based on the ability to directly quantify the intermolecular mobility in amorphous organic solids.

Second, the presence of increased mobility above T_β means that crystallization at these temperatures is facilitated, and storing amorphous materials at $T_g - 20$ K or $T_g - 50$ K may still not provide a stable environment for the glass, as shown for the case of naproxen. It should however be highlighted that the molecular mobility is facilitating rather than actively driving the structural changes and is not the only factor involved in the crystallization of amorphous materials.[44]

Some links between the secondary relaxations and nucleation were reported in the earlier work of Oguni et al.[12,13] The authors previously reported a possibility to resolve a secondary glass transition in molecular glasses at temperatures below T_g.[45,46]

In order to elaborate on this, we have performed a calorimetry study of all four drug samples, covering temperatures well below 0.67 T_g. We have found no change in the heat flow at temperatures below T_g. It is important to note in this context that Fujimori and Oguni used a very sensitive adiabatic calorimetry technique which is more sensitive than the technique used in our experiments.[47] The inability of standard DSC measurements to resolve T_β makes it impossible to use for routine sub-T_g analysis. While the sensitive adiabatic calorimetry measurements show clearly that there is a weak thermodynamic signature of a secondary glass transition in molecular glasses, the strong observation of T_β by THz-TDS hints toward a predominately kinetic nature of T_β, associated with a change in picosecond molecular dynamics. Given that T_β is much lower than T_g in the samples studied, it is highly unlikely to be related to the α-relaxation. This suggests that using the extrapolated primary relaxation time as a parameter to describe the molecular dynamics at temperatures significantly below T_g, regardless of whether this is based on dielectric or thermodynamic data, is unlikely to yield in a good stability parameter.

■ CONCLUSION AND OUTLOOKS

This study showed that the terahertz molecular dynamics is strongly related to the molecular mobility governing the stability of amorphous drugs. While molecular relaxations are often extracted by dielectric spectroscopy or DSC and used to predict the stability of the amorphous drugs, concerns have been raised about the robustness of these methods.[3,14] DSC is useful mainly for measurements of molecular mobility around and above T_g but cannot be easily used to measure molecular mobility at lower temperatures. Measurements by dielectric spectroscopy are very useful for measuring the local mobility in terms of JG-β relaxation, except for cases where this relaxation is submerged in the α-relaxation. In contrast, terahertz spectroscopy does not suffer from this limitation as it measures fast motions and only indirectly resolves the effect of the JG-β relaxation, which may in principle be observed even when no clear JG-β peak is present (such as in the case of indomethacin in this study). This emphasizes the robustness of terahertz/picosecond intermolecular dynamics analysis. Several different techniques, such as light scattering, neutron scattering, or optical Kerr effect can probe these dynamics as well, yet little focus has been given thus far to systematically examine any evidence of a change in molecular dynamics around 0.67 T_g. It would be however very valuable to do so in the future.

It is important to keep in mind that the terahertz analysis alone may not provide complete insight into all factors influencing the stability of amorphous materials. It however offers a very promising and easily accessible complementary analytical technique to more commonly used thermal and spectroscopic methods, offering an insight into the fast molecular dynamics that rule the physical stability and crystallization of amorphous materials.

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■ ASSOCIATED CONTENT

Supporting Information

XRPD of the storage stability tests of flufenamic acid, paracetamol, indomethacin, and simvastatin at 277 and 298 K as well as DSC characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.molpharmaceut.5b00330.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Hancock, B. C.; Zografi, G. Characteristics and significance of the amorphous state in pharmaceutical systems. *J. Pharm. Sci.* **1997**, *86*, 1−12.

(2) Petit, S.; Coquerel, G. In *Polymorphism*; Hilfiker, R., Ed.; Wiley-VCH: Weinheim, Germany, 2006; pp 259−286.

(3) Laitinen, R.; Löbmann, K.; Strachan, C. J.; Grohganz, H.; Rades, T. Emerging trends in the stabilization of amorphous drugs. *Int. J. Pharm.* **2013**, *453*, 65−79.

(4) Yu, L. Amorphous pharmaceutical solids: preparation, characterization and stabilization. *Adv. Drug Delivery Rev.* **2001**, *48*, 27−42.

(5) Marsac, P.; Shamblin, S.; Taylor, L. Theoretical and Practical Approaches for Prediction of Drug-Polymer Miscibility and Solubility. *Pharm. Res.* **2006**, *23*, 2417−2426.

(6) Zhou, D.; Grant, D.; Zhang, G.; Law, D.; Schmitt, E. Physical stability of amorphous pharmaceuticals: importance of configurational thermodynamic quantities and molecular mobility. *J. Pharm. Sci.* **2002**, *96*, 71−83.

(7) Andronis, V.; Zografi, G. Molecular Mobility of Supercooled Amorphous Indomethacin, Determined by Dynamic Mechanical Analysis. *Pharm. Res.* **1997**, *14*, 410−414.

(8) DiMartino, P.; Palmieri, G.; Martelli, S. Molecular mobility of the paracetamol amorphous form. *Chem. Pharm. Bull.* **2000**, *8*, 1105−1108.

(9) Kaushal, A. M.; Bansal, A. K. Thermodynamic behavior of glassy state of structurally related compounds. *Eur. J. Pharm. Biopharm.* **2008**, *69*, 1067−1076.

(10) Ambike, A. A.; Mahadik, K. R.; Paradkar, A. Physico-Chemical Characterization and Stability Study of Glassy Simvastatin. *Drug Dev. Ind. Pharm.* **2005**, *31*, 895−899.

(11) Fukuoka, E.; Makita, M.; Yamamura, S. Glassy State of Pharmaceuticals. III. Thermal Properties and Stability of Glassy Pharmaceuticals and Their Binary Glass Systems. *Chem. Pharm. Bull.* **1989**, *37*, 1047−1050.

(12) Okamoto, N.; Oguni, M. Discovery of crystal nucleation proceeding much below the glass transition temperature in a supercooled liquid. *Solid State Commun.* **1996**, *99*, 53−56.

(13) Hikima, T.; Hanaya, M.; Oguni, M. Microscopic observation of a peculiar crystallization in the glass transition region and beta-process as potentially controlling the growth rate in triphenylethylene. *J. Mol. Struct.* **1999**, *479*, 245−250.

(14) Bhattacharya, S.; Suryanarayanan, R. Local Mobility in Amorphous Pharmaceuticals − Characterization and Implications on Stability. *J. Pharm. Sci.* **2009**, *98*, 2935−2953.

(15) Grzybowska, K.; Paluch, M.; Grzybowski, A.; Wojnarowska, Z.; Hawelek, L.; Kolodziejczyk, K.; Ngai, K. L. Molecular dynamics and physical stability of amorphous anti-inflammatory drug: celecoxib. *J. Phys. Chem. B* **2010**, *114*, 12792−12801.

(16) Sokolov, A.; Kisliuk, A.; Novikov, V.; Ngai, K. Observation of constant loss in fast relaxation spectra of polymers. *Phys. Rev. B* **2001**, *63*, 172204.

(17) Ngai, K. L. Why the fast relaxation in the picosecond to nanosecond time range can sense the glass transition. *Philos. Mag.* **2004**, *84*, 1341−1353.

(18) Cicerone, M. T.; Douglas, J. F. *β*-Relaxation governs protein stability in sugar-glass matrices. *Soft Matter* **2012**, *8*, 2983−2991.

(19) Sibik, J.; Elliott, S. R.; Zeitler, J. A. Thermal Decoupling of Molecular-Relaxation Processes from the Vibrational Density of States at Terahertz Frequencies in Supercooled Hydrogen-Bonded Liquids. *J. Phys. Chem. Lett.* **2014**, *5*, 1968−1972.

(20) Parrott, E. P. J.; Zeitler, J. A.; Friščić, T.; Pepper, M.; Jones, W.; Day, G. M.; Gladden, L. F. Testing the Sensitivity of Terahertz Spectroscopy to Changes in Molecular and Supramolecular Structure: A Study of Structurally Similar Cocrystals. *Cryst. Growth Des.* **2009**, *9*, 1452−1460.

(21) Duvillaret, L.; Garet, F.; Coutaz, J.-L. A reliable method for extraction of material parameters in terahertz time-domain spectroscopy. *IEEE J. Sel. Top. Quantum Electron.* **1996**, *2*, 739−746.

(22) Suryanarayanan, R. In *Encyclopedia of Pharmaceutical Technology*, 3rd ed.; Swarbrick, J., Ed.; Informa Healthcare USA, Inc.: 2007; Chapter 290, pp 4103−4116.

(23) Zeitler, J. A.; Taday, P. F.; Pepper, M.; Rades, T. Relaxation and crystallization of amorphous carbamazepine studied by terahertz pulsed spectroscopy. *J. Pharm. Sci.* **2007**, *96*, 2703−2709.

(24) McIntosh, A. I.; Yang, B.; Goldup, S. M.; Watkinson, M.; Donnan, R. S. Crystallization of amorphous lactose at high humidity studied by terahertz time domain spectroscopy. *Chem. Phys. Lett.* **2013**, *558*, 104−108.

(25) Sibik, J.; Sargent, M. J.; Franklin, M.; Zeitler, J. A. Crystallization and phase changes in paracetamol from the amorphous solid to the liquid phase. *Mol. Pharmaceutics* **2014**, *11*, 1326−34.

(26) Löbmann, K.; Laitinen, R.; Grohganz, H.; Gordon, K. C.; Strachan, C.; Rades, T. Coamorphous Drug Systems: Enhanced Physical Stability and Dissolution Rate of Indomethacin and Naproxen. *Mol. Pharmaceutics* **2011**, *8*, 1919−1928.

(27) Strom, U.; Hendrickson, J. R.; Wagner, R. J.; Taylor, P. C. Disorder-Induced Far Infrared Absorption in Amorphous Materials. *Solid State Commun.* **1974**, *15*, 1871−1875.

(28) Taraskin, S.; Simdyankin, S.; Elliott, S.; Neilson, J.; Lo, T. Universal Features of Terahertz Absorption in Disordered Materials. *Phys. Rev. Lett.* **2006**, *97*, 1−4.

(29) Sibik, J.; Shalaev, E. Y.; Zeitler, J. A. Glassy dynamics of sorbitol solutions at terahertz frequencies. *Phys. Chem. Chem. Phys.* **2013**, *15*, 11931−11942.

(30) Tan, N. Y.; Zeitler, J. A. Probing Phase Transitions in Simvastatin with Terahertz Time-Domain Spectroscopy. *Mol. Pharmaceutics* **2015**, *12*, 810−815.

(31) Capaccioli, S.; Thayyil, M. S.; Ngai, K. L. Critical Issues of Current Research on the Dynamics Leading to Glass Transition Critical Issues of Current Research on the Dynamics Leading to Glass Transition. *J. Phys. Chem. B* **2008**, *112*, 16035−16049.

(32) Angell, C. A.; Ngai, K. L.; McKenna, G. B.; McMillan, P. F.; Martin, S. W. Relaxation in glassforming liquids and amorphous solids. *J. Appl. Phys.* **2000**, *88*, 3113.

(33) Ngai, K. L. *Relaxation and Diffusion in Complex Systems*, 1st ed.; Springer-Verlag: New York, 2011; p 835.

(34) Johari, G. P.; Kim, S.; Shanker, R. M. Dielectric studies of molecular motions in amorphous solid and ultraviscous acetaminophen. *J. Pharm. Sci.* **2005**, *94*, 2207−2023.

DOI: 10.1021/acs.molpharmaceut.5b00330
Mol. Pharmaceutics 2015, 12, 3062−3068

(35) Wojnarowska, Z.; Adrjanowicz, K.; Wlodarczyk, P.; Kaminska, E.; Kaminski, K.; Grzybowska, K.; Wrzalik, R.; Paluch, M.; Ngai, K. L. Broadband dielectric relaxation study at ambient and elevated pressure of molecular dynamics of pharmaceutical: indomethacin. *J. Phys. Chem. B* **2009**, *113*, 12536−12545.
(36) Graeser, K. A.; Patterson, J. E.; Zeitler, J. A.; Gordon, K. C.; Rades, T. Correlating thermodynamic and kinetic parameters with amorphous stability. *Eur. J. Pharm. Sci.* **2009**, *37*, 492−498.
(37) Qi, S.; Avalle, P.; Saklatvala, R.; Craig, D. Q. M. An investigation into the effects of thermal history on the crystallisation behaviour of amorphous paracetamol. *Eur. J. Pharm. Biopharm.* **2008**, *69*, 364−371.
(38) Correia, N. T.; Ramos, J. J.; Descamps, M.; Collins, G. Molecular mobility and fragility in indomethacin: a thermally stimulated depolarization current study. *Phar. Res.* **2001**, *18*, 1767−74.
(39) Allesø, M.; Chieng, N.; Rehder, S.; Rantanen, J.; Rades, T.; Aaltonen, J. Enhanced dissolution rate and synchronized release of drugs in binary systems through formulation: Amorphous naproxen-cimetidine mixtures prepared by mechanical activation. *J. Controlled Release* **2009**, *136*, 45−53.
(40) Löbmann, K.; Laitinen, R.; Grohganz, H.; Strachan, C.; Rades, T.; Gordon, K. C. A theoretical and spectroscopic study of co-amorphous naproxen and indomethacin. *Int. J. Pharm.* **2013**, *453*, 80−87.
(41) Kossack, W.; Adrjanowicz, K.; Tarnacka, M.; Kipnusu, W. K.; Dulski, M.; Mapesa, E. U.; Kaminski, K.; Pawlus, S.; Paluch, M.; Kremer, F. Glassy dynamics and physical aging in fucose saccharides as studied by infrared- and broadband dielectric spectroscopy. *Phys. Chem. Chem. Phys.* **2013**, *15*, 20641−50.
(42) Kipnusu, W. K.; Kossack, W.; Iacob, C.; Zeigermann, P.; Jasiurkowska, M.; Sangoro, J. R.; Valiullin, R.; Kremer, F. The interplay between inter- and intra-molecular dynamics in a series of alkylcitrates. *Soft Matter* **2013**, *9*, 4681.
(43) Sibik, J.; Korter, T. M.; Zeitler, J. A. Thermal changes in hydrogen bonding in amorphous sorbitol above and below T_g. Manuscript in preparation.
(44) Descamps, M.; Dudognon, E. Crystallization from the Amorphous State: Nucleation-Growth Decoupling, Polymorphism Interplay, and the Role of Interfaces. *J. Pharm. Sci.* **2014**, *103*, 2615−2628.
(45) Fujimori, H.; Oguni, M. Calrimetric study of D,L-propene carbonate: observation of the beta- as well as alpha-glass transition in the supercooled liquid. *J. Chem. Thermodyn.* **1994**, *26*, 367−378.
(46) Fujimori, H.; Oguni, M. Correlation index (Tga-Tgb)/Tga and activation energy ration as parameters characterizing the structure of liquid and glass. *Solid State Commun.* **1995**, *94*, 157−162.
(47) Fujimori, H.; Oguni, M. Construction of an adiabatic calorimeter at low temperatures and glass transition of crystalline 2-bromothiophene. *J. Phys. Chem. Solids* **1993**, *54*, 271−280.

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Mol. Pharmaceutics 2015, 12, 3062−3068