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A Study on the Characterization and Stability Implications of Investigating Local Mobility in Amorphous Pharmaceuticals

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ABSTRACT: There has been a deluge of research on the relationship between molecular mobility and the physical and chemical stability of amorphous drugs in recent years. Glass transition and global mobility-related molecular movements have been the primary targets of these investigations. There were, however, a handful of cases where the volatility could not be explained by international migration. The idea that b-relaxations, which occur at local scales well below the glass transition temperature, may be impacting stability is gaining traction. One common method for determining an amorphous pharmaceutical's mobility below the glass transition temperature (Tg) is to extrapolate data collected above Tg. While not well-suited to pinpointing precise local mobility, this kind of investigation may provide data about mobility in general. Our main goal from a pharmacological standpoint is to prove that local movements are important in amorphous drugs, especially in the Johari-Goldstein relaxations. In order to highlight the possible influence of local mobility on the stability of amorphous phases, an assessment of the coupling model was carried out that linked local movements with global mobility. We took into account the effects of water and other additives when studying the local movements in an amorphous matrix present in molecular dispersions. In conclusion, we have offered a concise review, highlighting the advantages and disadvantages, of the most widely used instrumental methods for characterizing local movements. To this day, Wiley-Liss, Inc., the publisher, has all rights.

Keywords: Amorphous, solid dispersion, lyophilization, mobility, and crystallization

INTRODUCTION

Pharmaceutical companies often produce amorphous forms of certain APIs used in drug formulation.1 An increasingly well-known problem that this method solves is the sluggish pace of dissolution caused by compounds' poor water solubility.1 As a result of their higher free energies, amorphous states may be less physically stable; crystallization tendencies are one indicator of this. Reduced chemical stability may also cause an intolerably short storage life. Thus, there is a lot of focus in the field right now on predicting stability and making amorphous pharmaceuticals. Investigators in the pharmaceutical industry have good cause to wonder if there is a link between molecular dynamics and the stability of amorphous phases.

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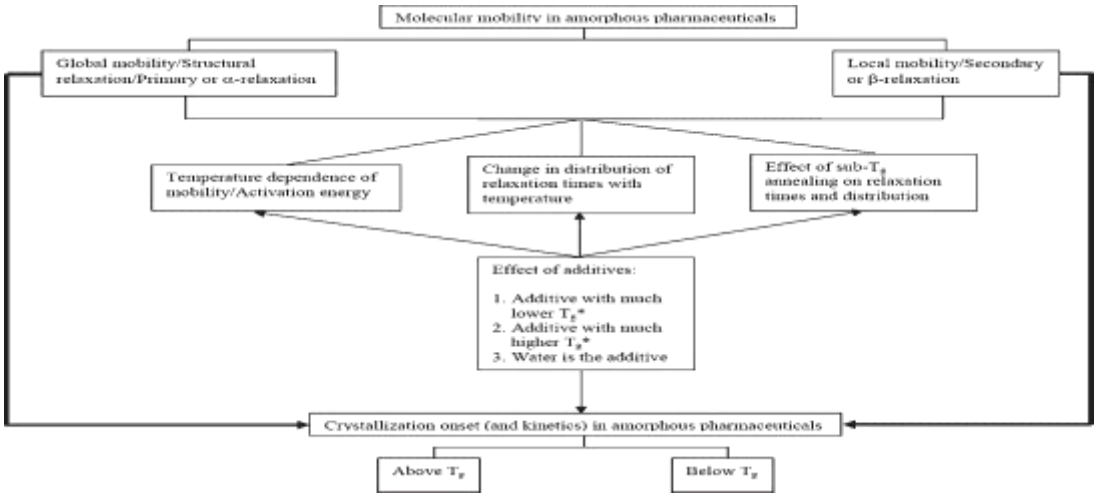
The temperature range for the glass transition determines whether an amorphous material exists as a solid or a supercooled liquid. The average relaxation time and viscosity of these materials varies by two to three orders.2 The mobility of the glass transition, or "global" mobility, is a key characteristic of porous materials that may have a close relationship to their possible physicochemical instability. Amorphous drug research has been heavily focused on the glass transition and its implications over the last 20 years.3-6 The glass transition temperatures (Tg) are not always a good indicator of an amorphous material's stability.7–9 In these cases, it was hypothesized that there was a direct relationship between the instability and the local mobility. Going beyond the glass transition and assessing the possible impacts of local molecule movements is necessary to comprehend the impact of molecular mobility on stability. Reasons why local mobility is crucial for chemical and physical stability include the following.

The traditional pharmaceutical shelf life is 4 years, although amorphous drugs may crystallize or show signs of nucleation when stored at far lower temperatures for substantially shorter periods of time.Both of those years.ten, twelve as a whole If crystallization is only caused by localized movements, it may still occur throughout the shelf life of the product, even at storage temperatures below (Tg — 50). The long-established view that mobility adds "negligibly" to instability may be invalid at temperatures below (Tg — 50)13,14. If you want to know when a chemical will crystallize, don't look at its glass transition temperature. The glass transition temperatures of nifedipine and felodipine are almost comparable, however the two exhibit very distinct crystallization behaviors.15

The crystallization kinetics of certain compounds were not controlled by the self-diffusion coefficient when temperatures approached Tg. The quick crystallization was thought to be caused by "local motions" rather than the structural relaxation period.16–20 Because of their local mobility, therapeutic macromolecules were unstable and prone to aggregation. However, stability was greatly improved upon by adding tiny molecules that limited local molecular movements.situations(8), (9), 21, 8.The glass transition is thought to start with local molecular movements, according to the substantial evidence.22 More recent studies demonstrating nucleation upon annealing at temperatures far lower than Tg, where it is insignificant, provide credence to the supposed importance of global mobility.7,12 Destabilization of an amorphous system may occur indirectly via the facilitation of global movement, even if local mobility is not the primary cause of instability in an amorphous matrix.

Despite local mobility's clear relevance as a prelude to glass transition, pharmaceutical researchers generally overlooked it up until recently. How local movements could impact the amorphous state's instability, namely crystallization, remained unknown as well. Experiments performed above Tg also yielded an additional consequence of molecular mobility below Tg.23 Measurements of mobility above Tg do not provide a sufficient explanation for the local mobility and noncooperative b-relaxation when applied to mobility below Tg.24 We want to demonstrate that, despite several outstanding questions about local movements, it is necessary to take into account both global and local mobility in order to comprehend the instability of amorphous medicines. Methods for measuring local mobility, its influence on stability and crystallization of amorphous pharmaceuticals, its link to glass transition, and the notion of secondary relaxation (more especially, Johari-Goldstein relaxation) have all been explored. Moreover, we have included some newer research on secondary relaxations in non-conformal medicinal systems.

A summary of the review's contents is given in the first scheme. Different variables may affect the mobility or crystallization of amorphous drugs, and we discussed the various forms of molecular mobility in this article. The pattern highlights the main point.



Scheme 1. Types of molecular mobility in amorphous pharmaceuticals and the effect of additives. Any mobility other than a-relaxation has been referred to as local mobility or b-relaxation. * with respect to the analyte.

review, i.e., the relationship between local and global mobility, and subsequently, mobility and crystallization. Furthermore, as described in detail later, the scheme shows the potential effects of additives on molecular mobility as well as crystallization in amorphous APIs.

COOPERATIVE a-relaxations on a global scale

A supercooled equilibrium liquid may be formed when a liquid is cooled rapidly below its melting point; this kind of liquid has characteristics like a viscosity below 1012 Pa s and a structural relaxation time below 100 s. If the supercooled liquid does not crystallize at a temperature where the observational timescale is equivalent to the structural relaxation period, it will undergo glass transition. According to what Cohen and Turnbull said, the free volume of a super-cooled liquid decreases as its temperature decreases, with Tg being the lowest limit.3 This glassy state undergoes a very little change in free volume during cooling, in comparison to supercooled liquid. As Tg approaches, the structural relaxation time, the amount of time it takes for molecules to diffuse across an inter-particulate distance, increases, and in order to alter relative positions, more cooperation between nearby molecules is needed.2 Hence, the glass transition is caused by coordinated molecule movement, often known as "global mobility." The term "a-relaxations" may describe how these molecular motions show up in dielectric relaxation profiles at lower frequencies.25 As can be seen from Figure 1, the structural relaxation time as a function of temperature is well explained by the Williams-Landell-Ferry and Vogel-Tammann-Fulcher (VTF) models.26 Structures relax with less activation energy at higher temperatures because of the glass transition. The reason for this is because the barrier to molecular mobility is reduced as the free volume increases.

Implications of a-Relaxation

Transition from the glassy to supercooled liquid state upon heating results in a dramatic increase

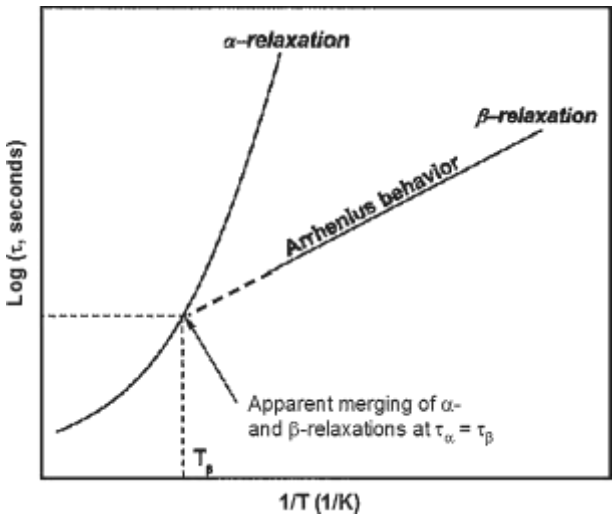


Figure 1. Schematic of the temperature dependence of a- and b-relaxations (modified from Ref. 127). Note that at T_b, the two relaxations merge.

shorter time it takes for structures to relax, suggesting more mobility. Because of the subsequent effect on diffusion, nucleation and subsequent crystal growth might be feasible. The cooperative a-relaxations of an amorphous molecule may be enhanced by adding a plasticizer, an additive having a lower Tg. In this context, the phrases "plasticizer" and "antiplasticizer" refer to additives that alter the global mobility within a host matrix. A brief explanation would be that plasticization implies an increase in molecular mobility and antiplasticization signifies the inverse. The generalized concepts will be used within the context of local mobility. At 136 K, water has a glass transition temperature (Tg), making it a widespread plasticizer. One of its biggest issues in the pharmaceutical sector is the effect it has on physical and chemical stability.28, 29 Amorphous compounds may be stabilized by adding an antiplasticizer, a high Tg ingredient.30

Since amorphous drugs often have aging effects when stored below Tg, the annealing process has a substantial impact on a-relaxations. The storage temperature (~Tg) of a drug may impact its worldwide mobility, which might have implications for its therapeutic properties. The effects of aging on the rate and extent of water sorption are of considerable practical importance.31 In addition, the decreased global mobility that accompanies aging may improve chemical stability.integers 32 and 3

LOCAL MOBILITY (NONCOOPERATIVE b-RELAXATIONS)

Glassy systems exhibit intramolecular reorientations, which include the whole molecule and are referred to as "local mobility" or b-or second-ary relaxations.34 These kind of relaxations, in contrast to a-relaxations, do not need collaboration and usually last anywhere from a few tenths of milliseconds to a whole second. The movement of side chains inside a polymer is an example of an intramolecular motion. The Johari-Goldstein relaxations, which are noncooperative secondary relaxations, will be studied in detail since they are present in all organic small molecule glasses.36 In contrast to a-relaxations, b-relaxations typically follow Arrhenius kinetics and have much lower activation energy values at temperatures around or below Tg.25,37 With increasing temperature, the a-38,39 and b-relaxation40 periods shrink and their distributions becoming more compact. The a- and b-

relaxations combine at a certain temperature (Tb) greater than the Tg when the relaxation periods are the same, as seen in Figure 1. We estimate that, according to dielectric spectroscopy, the a- and b- relaxations merge in different glass formers at a frequency (nmax) of about 6.5.41 log10(nmax/Hz). To get a relaxation time of 5 × 10—8 seconds, this equation is used.

Relaxations known as Johari-Goldstein

Up until the early 1970s, the conventional wisdom was that secondary relaxations were caused by intramolecular motions stemming from restricted rotation around chemical bonds, including the rotation of polymer side chains.42 On the other hand, Johari and Goldstein demonstrated that secondary relaxations may occur even in rigid molecules devoid of internal degrees of freedom. These findings laid the groundwork for what is now known as Johari-Goldstein (JG) relaxations, which include the complete molecule's motion and represent a kind of secondary relaxation.3, 6, 4, 5. The precise nature of these relaxations is still a point of contention for many. Although there are those who believe that every single molecule in the system is consistently engaged in these motions in some way,45–48 Johari claims that these motions can only be performed on certain parts of the eyewear.49 As the antecedent of the cooperative a-relaxation, the JG relaxations have been a mystery to the Ngai22 extended coupling model, which has attempted to shed light on their origin. Although several individuals have differing opinions on the origins of the local movements, we will still provide a brief overview of this model below.50, 51, 46–48

According to Ngai's theory, there are three separate time regimes in the dynamics of supercooled liquid molecules: the short, intermediate, and long. The short-time regime is characterized by "caged" relaxation units that display only vibrational motions and a little change in the function exp(—t/t), where t is the observation time and t is the relaxation period. Noncooperative independent relaxations, also called "primitive" a-relaxations, and exponentially decreasing relaxation durations define the intermediate-time regime. Furthermore, cooperativity is increasing continuously due to the fact that relaxing units are interacting with each other in a two-way fashion. The stretch exponential function exp(—t/t)bKWW defines the long-time regime of slower cooperative a-relaxations; bKWW is a measure of the divergence from exponential decay and the governing equation is Kohlrausch-Watts. As a conceptual bridge between the autonomous relaxations and the cooperative a-relaxations, there exists a time interval tc that is independent of temperature. The relaxations happen independently for durations less than tc, but they transform into cooperative slower a-relaxations due to intermolecular interactions for durations greater than tc. As shown for glass-forming polymers by quasielastic neutron scattering52,53, the value of tc for small molecule organic glass formers may likewise be around 2 ps.39. It is possible to estimate the independent relaxation time, t0, using empirical correlations with the a-relaxation time.

, t_a, at T_g[39]:

$$t0 = t_a^{bKWW} \times t^{(1—bKWW)}$$

It has been proposed that some glass formers may be precursors to cooperative molecular motions based on their JG relaxation times, which are comparable to the expected values of non-cooperative independent relaxation times.54 Looking at the JG relaxations from this angle makes their drug-related implications more apparent. Therefore, to fully comprehend the molecular mobility in an amor-phous matrix, it is essential to characterize the JG relaxations in detail.

In a system with several secondary relaxations, locating the JG relaxations is of the utmost importance. Classification of secondary relaxations is based on their dynamical properties.54 For a relaxation to be classified as JG, its temperature and pressure dependency tendency have to be similar to that of an a-relaxation. Additional relaxations were identified as JG relaxations when the independent relaxation timings matched the measured b-relaxation durations. It was observed that JG

relaxations were more severely affected by glass aging than non-JG relaxations. The premise upon which all these discoveries are based is that JG relaxations include the mobility of the whole molecule. A "pseudo" JG relaxation as well as a true one were shown for tripropylene glycol.54 It was argued that the "pseudo" JG relaxation included both the molecule-wide and intramolecular motions, as it showed some similarities with the true JG relaxation. The foundation of cooperative movements are JG relaxations, making this kind of research vital. Kaminski et al.55 discovered that the slower secondary relaxations in various monosaccharides, which change with pressure, are the actual JG relaxations. Ngai et al.54 suggests that the faster "pseudo" JG relaxations in tripropylene glycol could be due to hydrogen bonding.56 After studying the effect of temperature on hydrogen bonding during glass transition using vibrational spectroscopy (e.g., FTIR or Raman), the role of hydrogen bonding in global mobility may be better grasped.57 Future studies on the local mobility of small, amorphous organic molecules that may have medical uses should look at the impact of hydrogen bonding, if any.

Varieties in the Range of b-Relaxation Durations

Due to changes in local density or free volume, molecular motions in a supercooled liquid become spatially heterogeneous59 and dynamically heterogeneous58 as the glass transition is approached. Thus, there is both spatial and dynamic heterogeneity; the former manifests as regions with sections of fast-and slow-relaxing molecules, respectively, while the latter shows a wide range of relaxation durations for molecules. This is why relaxation times in glass are much more unpredictable than in supercooled liquid. Consequently, the distribution of b-relaxation durations in a glass is more scattered than that of a-relaxation durations.41 In a wide variety of materials, the distribution of a- and b-relaxation durations is correlated with fragility.41 The dielectric b-relaxation peak, which shows the distribution of b-relaxation periods, was somewhat related to the fragility (m) of different glass formers (Fig. 2).41 There found a much stronger correlation for a-relaxations. It was shown that the distribution of a-relaxation times is inversely related to fragility; in other words, structural dynamics heterogeneity increases as material fragility rises. Strangely, glass formers seem to be delicate based on the way they crystallize.60 Some glass formers exhibit a sharp increase in the crystal growth rate around Tg upon cooling of the supercooled liquid.61 The apparent quickening of the crystal growth rate could not be explained by diffusion. The fact that the fragility of the liquid determines the degree to which the self-diffusion coefficient of a glass-forming liquid decouples from an inverse scaling with viscosity certainly holds the key to the answer.60 Theoretically, the fragility is related to the increasing dynamic and spatial heterogeneity of molecular motions as Tg is approached during cooling of the supercooled liquid.

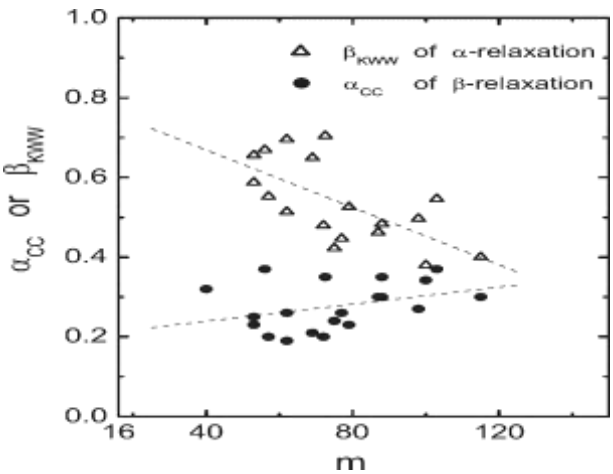


Figure 2. Change in distribution of a- and b-relaxa- tion times with fragility (m) of different glass formers. b_{KWW} is a measure of a-relaxation time distribution while a_{CC} describes distribution of b-relaxation times. (reproduced from Ref. 41).

Crystallization kinetics speed up as a consequence of increased decoupling from the inverse connection with viscosity. Since a-relaxations are too sluggish to account for the crystal growth rate, local movements are believed to have a significant role in this phenomena, as will be explained later.61

A- and b-Relaxation Energy Landscape Comparisons

The mechanism behind these motions, which may be described as cooperativity or its absence, is clearly related to the much greater activation energies of a-relaxations compared to b-relaxations25. As is known, b-relaxa-tions change their heat capacity at a certain transition temperature, similar to the glass transition. Reduced heat capacity is a result of these transitions' weaker nature compared to the glass transition.Here we have 62,63 As seen in Figure 3, the potential energy landscape exhibits a global minimum for the a-relaxation, which includes the secondary relaxations as local ones. The distinct configurations achieved by molecular reorientation and limited translational motion correspond to each of the shallow minima for the b-relaxation.49 The distribution and placement of shallow potential energy barriers, as well as the quantity of molecules in a given configuration, are all dictated by the material's thermal history.64 As one ages, this impact would likewise become more pronounced. As we age, our energy and stamina naturally decline.

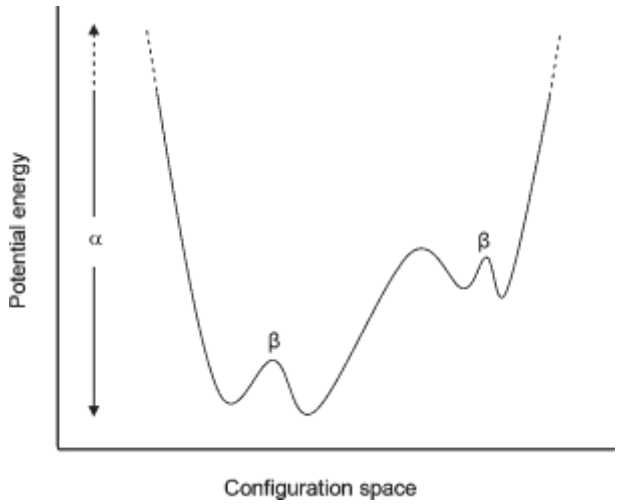


Figure 3. Schematic representation of potential energy landscape of a- and b-relaxations (adapted from Ref. 64).

and entropy. In other words, the energy barrier of the global minimum for a-relaxation increases upon aging.[49] The contribution of b-relaxations to configurational entropy also decreases upon aging indicating an increase in the energy barrier of the b-relaxation local minima or a decrease in the number of minima.[49]

The Impact of Age on the Characteristics of b-Relaxation

The terms aging and annealing have been used interchangeably in the literature to describe the same process—the glassy state relaxing at a fixed temperature over time.

Donth65 has attempted to distinguish between the two ideas, and his position is that aging is an unintended consequence that leads to relaxation. However, annealing glass is an intentional process that yields certain results. Following these clarifications, we will use the terms. The lyophilization and other methods used to prepare and store amorphous pharmaceuticals cause them to age. An annealing procedure might potentially simulate this aging effect. Research on molecular mobility in amorphous medicinal materials need to focus on how annealing affects the properties of a- and b-relaxations. The enthalpy, volume, and entropy of a glassy matrix all decrease as it matures. Consequently, there is less global mobility and cooperative movements are becoming more diverse.66 On the other side, we know that b-relaxation durations and distribution heterogeneity tend to go down, 67–70. This indicates that there is a general trend toward faster and more uniform local movements. Annealing does not significantly alter the distribution of b-relaxation times, however. The seemingly counterintuitive quicker b-relaxation duration after annealing is caused by the nonuniform collapse of "islands of mobility."70 Overall, the distribution would become smaller and shift to shorter periods due to because of this nonuniform collapse, regions with longer relaxation durations kinetically freeze. Annealing amorphous pharmaceuticals may increase their chemical stability.71 In this case, the chemical instability was linked to the fact that annealing decreased the global mobility. Be warned, however, that when stability and local mobility coexist, this strategy would bomb. As stated before, this is due to the fact that annealing does not inhibit local motions. Contrarily, it seems that local mobility has grown as the a-wind downs.

PHARMACOLOGICALLY IMPORTANT SYSTEMS AND SECONDARY RELAXATIONS

Table 1 displays a range of systems, from the most basic to the most complex, with several components. Consideration of the instances' potential pharmacological significance led us to categorize them as either single-component or multi-component systems. The impact of water was investigated separately since it is a ubiquitous additive that significantly affects molecular mobility. All right, I'll give you some examples now.

Systems with Just One Part

Secondary relaxations have been studied in polymers extensively and have been seen as peaks in loss modulus versus frequency graphs in dielec-tric spectroscopic research. The Greek letters (b, g,...) indicate the decreasing or increasing frequency in relation to a specific temperature.85 The inhibition of side chain rotations, such -COOCH3 in polymethyl methacrylate (PMMA), was formerly believed to be the primary cause of these secondary relaxations.42 Secondary relaxations in linear polymers, such as polyvinyl chloride, are believed to have originated from localized vibrations of the polymer backbone.42 As previously stated, the pharmaceutical sector stands to benefit greatly from the discoveries made by Johari and Goldstein, who showed that some small chemical molecules had secondary relaxations. Isomeric octanols and butanols44, as well as o-terphenyl, were among the nonrigid compounds in which these authors documented secondary relaxations.36

Many active medicinal components and excipients are characterized by specific interactions, such hydrogen bonding. Local changes in the glassy state and the influence of specific interactions inherent to the molecular structure of amorphous substances are important for medicinal purposes. Dipropylene glycol dimethyl ether (DPGDME) and dipropylene glycol (DPG) were shown to be involved in hydrogen bonding in their molecular dynamics.86 The second molecule lacks hydrogen bonding, despite their structural similarity. The range of a-relaxations was narrower in DPG.

The Impact of Subsequent Relaxations on Additives

The "local" molecular mobility of a multi-component amorphous matrix would vary from that of its individual components, which is significant since pharmaceutical formulations commonly consist of many components. This includes relaxation

durations and how they are affected by temperature. Hence, from a pharmacological standpoint, it is essential to understand the local mobility of systems with several components. Table 1 displays the results of several investigations. Here we shall discuss some of the most noteworthy findings in detail.

Secondary relaxations, specifically JG relaxations, in multicomponent single phase glassy systems containing a range of rigid small organic molecules were thoroughly examined.36 Goresy et al.90 compared the b-relaxations of solid dispersions of nifedipine and acetaminophen with those of the pure components and found that the presence of acetaminophen had minimal effect on the activation energy of fast, probably intramolecular relaxations in nifedipine. Since the glass transition is believed to follow the JG relaxations, distinguishing between the two is of the utmost importance.

delineate these gradual changes from others that would not influence the amorphous medication's stability. The secondary relaxation processes were shown to be additive in di-n-octyl phthalate, di-isooctyl phthalate, and their mixes, indicating that they could originate inside the molecules themselves. Consequently, we labelled these relaxations as deviating from JG relaxations.78 Yoshioka et al.8 examined the stability of glassy insulin colyophilized with trehalose or dextran in regard to b- relaxations. Compared to the insulin-trehalose system, the insulin-dextran system deteriorated more quickly because trehalose inhibited b-relaxations but dextran did not (Fig. 4B).

It has been investigated how plasticizers affect the local mobility of amorphous substances. The plasticizing effects of trehalose on local movements are offset by glycerol, which promotes global mobility21,76, which goes against predictions. These findings have huge ramifications for the development of new pharmaceutical formulations. If protein instability is associated with local motions, then the local movements of the glassy matrix in a lyophile containing amorphous excipients would have an immediate effect on protein stability. The antiplasticizing effect of glycerol on the local trehalose motions was temperature dependent.77 This threshold temperature was shown to have an inverse connection to the glycerol content. With lower glycerol concentrations and higher temperatures, antiplasticization would occur. According to these studies, the mobility of the system is dictated by the relative concentrations of the excipients. Pharmaceutical dosage forms manufactured as molecular dispersions may have varying amounts of active pharmaceutical ingredients (APIs) per dose. There are usually a lot of parts and excipients in these systems. One example is a lyophilized powder that has to be reconstituted before it can be delivered. It may be required to modify exci-pient relative concentrations to decrease system mobility due to variations in API content per dose. We begin with the assumption that motion influences stability in this line of thinking.

Impact of Subsequent Relaxations on Glassy Drugs by Water

A solid dosage form's components' physical and chemical stability may be affected by water.28, 29 Extensive research has focused

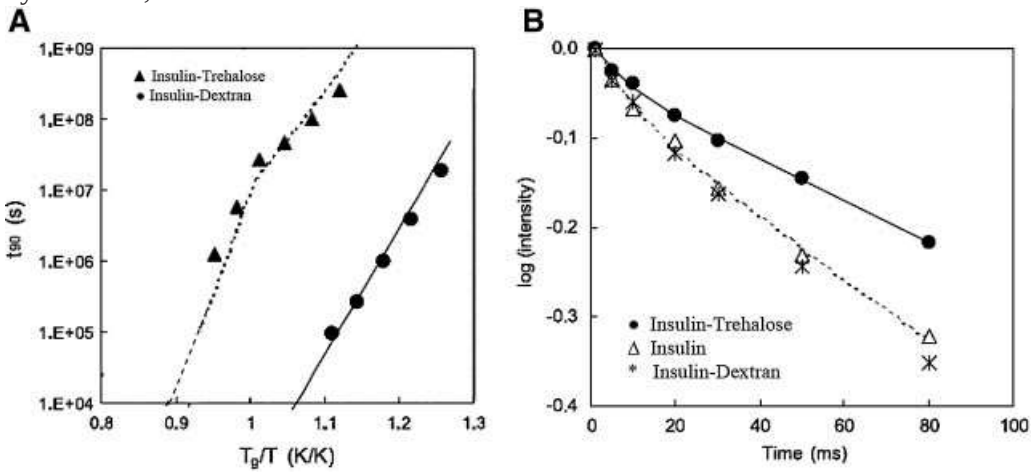


Figure 4. (A) T_g scaled temperature dependence of the time required for 10% degra- dation of insulin, t_{90}, at 12% RH in lyophilized formulation with trehalose or dextran;
(B) rotating-frame spin-lattice relaxation intensities for insulin carbonyl carbon as a function of time in lyophilized insulin, insulin–dextran and insulin–trehalose at 258C and 12% RH (adapted from Ref. 8).

for inorganic pharmaceuticals and the "plasticizing" effect of water. Plasticization is the process that occurs when the glass transition temperature falls and global mobility rises. While it's common knowledge that water acts as a plasticizer and helps with the glass transition, studies investigating its effects on local mobility are few. Brulez et al.79 used dynamic mechanical analysis to determine that the temperature of secondary relaxations reduced as the water content in glassy starch rose. It is interesting to mention that adding sucrose to the starch-water matrix raised the temperature of secondary relaxations, indicating that specific interactions are important for deciding the impact on local motions. What occurred when lyophilized carbs interacted with any residual water was the subject of research by Moznine et al.80. The faster noncooperative dielectric relaxations, mediated by a protonic charge transfer mechanism in the presence of water, dictated the rates of sugar degradation, they discovered. Water has no impact on the duration of sorbitol's b-relaxation periods but does affect the strength of that relaxation, suggesting that the hydrogen bonding networks of the two substances are similar (Nozaki et al.81). Water affected the b-relaxation strength of xylitol94, much as it did other low molecular weight carbohydrates82. As the water concentration in poly(vinylpyrrolidone) grew, so did the activation energy for b-relaxations.Page 83

In other words, the antiplasticizer actions of water mitigated the localized motions in poly(vinylpyrrolidone). It was shown that molecular shape is one of the processes regulating local mobility in low molecular weight carbohydrates.82 As Swenson et al.84 have out, myoglobin undergoes secondary relaxations in glycol-water combinations. They proved that local protein motions are caused by the noncooperative solvent movements at low temperatures. This discovery has the potential to impact the physical stability of peptides or proteins when they are freeze-dried.

The Effects of b-Relaxations on the Stability of Small and Large Molecules

Amorphous medicine's physical stability has been the subject of several recent studies that have sought to define the role of sub-Tg secondary relaxations. Crystallization of many substances has been seen below their corresponding Tg values. Among these compounds are salol, o-terphenyl, and triphenylethylene,17,18. The findings are in agreement with those of Scherer et al.95, who also discovered that o-terphenyl crystallizes at a faster rate close to Tg. The crystallization mechanisms of salol and o-terphenyl were characterized by Hikima et al. based on homogeneous nucleation.18, 17: They hypothesised that "crystal embryos"—structured molecular aggregates that could form at lower temperatures and then, as a result of a drop in interfacial tension, were incorporated onto the surface of the growing crystals. It seems that the b-relaxation durations affected the crystal growth rates of triphenylethylene, as the predicted and experimentally observed crystal growth rates were quite congruent. This research shows that b-relaxation mechanisms regulate crystal growth in triphenylethylene, o-terphenyl, and salol.

Additional evidence that local mobility may impact crystallization was reported by Ishida et al.96 in their study of amorphous nifedipine, which revealed a sudden shift in crystal form and crystal growth rate at Tg. Furthermore, crystal growth rate was unaffected by nifedipine solid dispersion with PVP at (Tg + 50), while it was affected one hundred times less at Tg (Tg + 9). As previously stated, nifedipine and felodipine have

Despite having almost identical Tg values (~428C), felodipine has a much greater resistance to crystallization than nifedipine.fifteen, eleven Bhugra et al.11 found a large curvature in a log-log plot that

shows the relationship between the timings of crystallization start and the durations of dielectric relaxation in amorphous nifedipine near Tg. The curvature shows that the crystallization start times are much sooner than expected. There was no similar curvature in felodipine. Based on these findings, b-relaxations may play a role in the easier crystallization of nifedipine compared to felodipine. Sun et al.61 recently investigated the crystallization of several ROY polymorphs when the supercooled liquids were cooled. A much faster crystallization mode was seen just above the Tg. Further data on o-terphenyl's self-diffusion coefficient and crystal growth rate were gathered from various sources to prove that the fast acceleration of the crystal growth rate near Tg was not due to diffusion (Fig. 5). These findings corroborate those of Hikima et al.,17,18; however, the faster crystallization mode was already apparent for ROY polymorphs above Tg. According to Sun et al.61, a-relaxation cannot aid molecule transport to the growing crystal due to the fast crystallization close to Tg. Therefore, it was presumed that local motions or the b-relaxations were responsible for this faster crystallization phase. The nucleation of domethacin further supported the idea that crystallization is a direct result of underlying local motions.

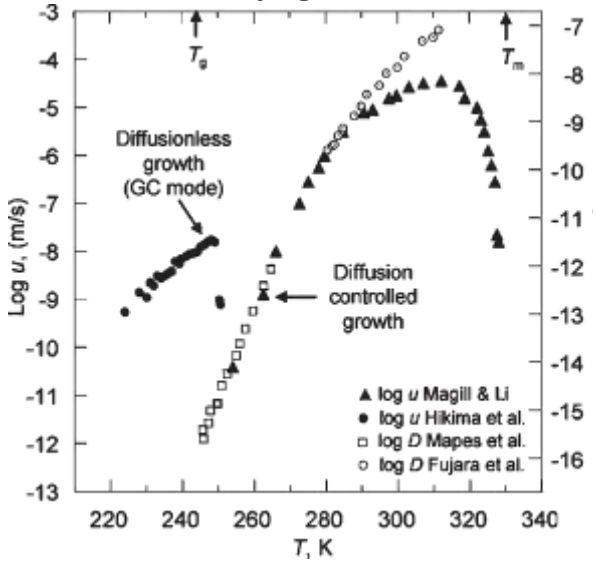


Figure 5. Temperature dependence of crystal growth rate and self-diffusion coefficient in supercooled liquid of *o*-terphenyl showing the failure of diffusion to explain sudden increase in crystal growth rate near T_g (reproduced from Ref. 61).

after 147 days of storage at (Tg—55).7 It was shown that the critical nucleus size of crystalline indomethacin was less than the cooperatively rearranging area, suggesting that critical nuclei may be formed by local movements alone.12

Nevertheless, there is a dearth of research that proves b-relaxation affects crystallization. Using dielectric spectroscopy, Alie et al.16 sought to directly connect global and local mobility with crystallization by studying the temperature dependence of a- and b-relaxation and the crystallization durations of a low molecular weight molecule above Tg. It was discovered that the b-relaxation and crystallization periods showed comparable temperature dependence. This finding led to the conclusion that the crystal development was caused by b-relaxations. As we have shown, physical stability below and above Tg may depend critically on local mobility.

The Interaction Between Chemical Stability and b-Relaxations

No comprehensive research on the relationship between chemical instability and local mobility in small molecules has been conducted as far as we are aware. A short overview was provided by Yoshioka et al. (97), who mainly focused on macromolecules, regarding the relationship of secondary relaxations with chemical stability. Some proteins' chemical stability may be determined by their local mobility, according to research by Strickley et al. (1998) and Chang et al. (99, 100). Afterwards, Yoshioka et al. used 13C solid-state NMR spectroscopy to show that local mobility correlates with insulin8 breakdown and b-galactosidase aggregation. Glycerol and other "plasti-cizers" may stabilize proteins by inhibiting local movements, as previously shown by Cicerone et al.21,76 When developing stabilization techniques for medicinal macromolecules, these results are crucial.

METHODS USED IN INSTRUMENTS

RESEARCHING SECONDARY RELATIONSHIPS

The analytical methods that were used to investigate molecular mobility, together with their underlying principles, benefits, and drawbacks, are outlined in Table 2. With a focus on dielectric relaxation spectroscopy, this section provides more detailed information along with examples from the literature.

Table 2. Commonly Used Techniques to Characterize Local Mobility

Techniques	Principle	Limitations	Usefulness
Differential scanning calorimetry	Measurement of heat flow associated with thermally induced transitions	(i) Expensive instrumentation (ii) Specialized and usually dedicated expertise (iii) Long data collection time	local mobility
Quasielastic neutron/light scattering	Measurement of changes in incoherent scattering function with scattering vector	(i) Interference from conductivity at low frequencies (i) Reproducibility	Possible to simultaneously study local and global mobility as well as crystallization
Dielectric relaxation spectroscopy	Reorientation of dipoles under the influence of electric field of variable frequency	(i) a- and b-Relaxations in small and macromolecules using variable frequency or temperature (ii) Various models to fit spectra (iii) Direct determination of relaxation times and their distribution	(i) Ease of data collection and analysis (i) Information about fast high frequency molecular dynamics (ii) Determination of crossover between faster and slower relaxations
Thermally stimulated depolarization current	Reorientation of dipoles by electric field followed by quenching to ‘‘freeze’’ the orientations and subsequent measurement of depolarization current during heating	(i) High sensitivity to small currents corresponding to low frequency molecular motions (ii) Resolution of overlapping events	(i) Indirect and limited information about local mobility (ii) Lacks sensitivity in measuring local mobility (i) Interference from fast vibrational motions
Nuclear magnetic resonance	Measurement of the emission of absorbed radio frequency radiation by nuclei in presence of an external magnetic field	(i) Determination of origin of molecular motions (ii) Correlation between chemical stability and	(ii) No direct information about relaxation time distribution (iii) Specialized expertise in data collection and analysis
Diathermal Resonance Spectroscopy	The most effective method for characterizing secondary relaxations in many different materials is dielectric relaxation spectroscopy, which can differentiate between slower cooperative dynamics and quicker noncooperative	(i) Resolution of overlapping	

dynamics.104 and beyond We may readily collect information regarding relaxation timings, relaxation strength, peak broadening, and asymmetry characteristics from the appropriate mathematical models that have been created and verified for fitting dielectric relaxation data.101,105 For dielectric relaxation processes, the Debye function is the fundamental model function: A function that combines Cole-Cole and Cole-Davidson is called the Havriliak-Negami function:

$$o^{*}(v) = o_{\infty} + \frac{Do}{(1 + (ivt)^{b})^{g}}$$

By fitting the dielectric spectra with the Havriliak-Negami model, Power et al. determined the aforementioned parameters and demonstrated that JG relaxations result from the molecular reorientation of "isl ands of mobility" rather than from the small-angle motions of every single molecule.70

$$o^{*}(v) = o_{\infty} + \frac{Do}{1 + ivt}$$

$$o^{*}(v) = o' + o''(v)$$

where e'(v) is the integral component of the complex dielectric function that describes the energy stored in the medium and e"(v) is the imaginary part, which represents the energy dissipated in the medium and is also called dielectric loss. The dielectric strength or intensity, denoted as (es — e∏), is determined by the static permittivity or the low frequency limit (v → 0) of e'(v) and the high frequency limit (v → ∏) of e'(v). Here, v is the frequency, t is the relaxation period, and De is the result. The Debye model predicts that the dielectric loss vs frequency profile will have a symmetric peak, with a finite full width at half maximum of 1.14 decades. You may get the greatest relaxation time (tmax) by using the formula tmax = (1/2)pfmax, which takes into account the frequency that corresponds to the highest dielectric loss. The peak width is a direct measure of the distribution of relaxation times. The majority of the time, dielectric relaxation peaks are both wide and uneven. The Cole-Cole function describes the peak broadening:

$$o^{*}(v) = o_{\infty} + \frac{Do}{1 + (ivt)^{b}}$$

where the parameter b describes the symmetric peak broadening and the range of values for b is from 0 to 1. The Cole-Davidson function, however, provides a description of asymmetric peak broadening:

Current Stimulated by Heat

(TSC)

Ionic thermoconductivity was suggested by Bucci and Fieschi 106 as a way to investigate polarization in semiconductors. When used on nonionic chemicals, this method evolved into thermally stimulated current 107 (TSC). Amorphous drugs have been characterized using it, and studying molecular mobility in the amorphous phase has shown to be its most fruitful use.10, 16, 87, 88, 108–112 Applying an electric field to the sample at a certain temperature causes dipolar reorientation, which is one of the TSC approaches. This technique is known as thermally stimulated depolarization current (TSDC). After that, the dipolar orientations are "frozen" by quenching the sample, and the depolarization current, which is measured during heating, is used to determine the molecular mobility. Alie et al. showed that TSDC is well-suited to investigate mobility below the Tg, while DRS is useful for studying mobility above the Tg, therefore TSDC may be a wonderful complementary tool to DRS.16 One potential application of TSDC's fractional polarization approach is to selectively activate dipoles in order to learn more about small populations of relaxed species.112 One similar but less common method is thermally stimulated polarization current (TSPC), which involves applying an electric field at a low temperature, a region with limited dipole mobility, and then polarizing the dipoles.

when the temperature is raised.113 In contrast to TSDC, TSPC

$$o^{*}(v) = o_{\infty} + \frac{Do}{(1 + ivt)^{g}}$$

The benefit of studying a material with little impact on its thermal history has been used in cases where the asymmetric broadening parameter, denoted as g, has a value between zero and one. Combining the to describe local movements in pharmaceutical macromolecules is the general model.113

Radioactive Isotope Mapping

The method of nuclear magnetic resonance (NMR) has already been covered extensively elsewhere, and its explanation is beyond the purview of this article. Research on b-relaxations in pharmaceutically relevant substances has made use of 114 NMR. By using one- and two-dimensional two-dimensional nuclear magnetic resonance (NMR), Vogel et al. investigated the process of JG relaxations in both small molecules (like toluene and glycerol) and macromolecules (like polybutadiene and polystyrene). To investigate the relationship between glassy-state local mobility and crystallization behavior, solid-state 13C NMR was used.115 The chemicals that served as models were salicin and Indomethacin. Water sorption's impact on sucrose and PVP matrices' local mobility was investigated by Aso et al.116 Using 13C NMR, we investigated the molecular dynamics of sorbitol and maltitol to determine why their a- and b-relaxations above their T lysozyme were different.number 121. Light scattering was also a feature of the quicker relaxations in picoline and glassy toluene.122 The authors Pravinata et al.123 investigated local mobility and dynamic heterogeneity in amorphous sucrose by means of time-resolved erythrosine B phosphorescence. The heterogeneous dynamics of JG relaxations in glassy sorbitol were studied by Richert124 using the dielectric hole-burning method. The

impact of free volume on local mobility in amorphous pharmaceutical systems could be better understood with the use of positron annihilation lifetime spectroscopy (PALS), a technique that has been used to characterize structural relaxation126 and local mobility125 in polymers depending on changes in free volume but has not been investigated thus far.

Researchers in the pharmaceutical indstry have access to a wealth of resources that allow them to study the local mobility of organic compounds including tiny molecules. While dielectric spectroscopy has been the main tool up until now, Yoshioka et al.8,9,97 demonstrated that by using other techniques simultaneously, we can get complementary information that aids in understanding local mobility.

Thermo-Scanning Differential (DSC)

Conventional DSC may be used to analyze b-relaxations in amorphous systems of tiny organic compounds, as recently shown by Vyazovkin et al.7,12,24,27,118. To determine the b-relaxations, which are more common below Tg than around Tg, one may anneal amorphous systems at around 0.8 Tg24, then rapidly cool and reheat them to get shallow enthalpic recovery endotherms just before Tg. The enthalpic recovery peak moves to higher temperatures when the annealing duration is increased. Inorganic glasses were the subject of a thorough investigation by Chen119 into this phenomenon. In polymers, Bershtein and Egorov120 demonstrated the similar result and determined the activation energy by relating the peak temperature (Tp) to the heating rate (q).

$$E = -R \frac{d(\ln q)}{d\left(\frac{1}{T_p}\right)}$$

Other Techniques

More specifically, we used quasielastic neutron and light scattering techniques to learn how hydration affected the faster molecular dynamics. Additionally, the sensitivity, sample size, and amount of information needed might impact the approach selected.

CONCLUSIONS

The majority of the research on the topic of amorphous pharmaceutical molecular mobility and stability has been on either global mobility or a-relaxations. In several cases, however, such mobility has not been sufficient to explain instability; for instance, crystallization at temperatures far below the glass transition temperature is one such example. New research in the field of amorphous medicines has shown a connection between local mobility and chemical and physical instability. One important factor in the physical stability of amorphous phases is local mobility or secondary relaxations, particularly JG relaxations. Some believe that the JG relaxations impact global mobility since they are the antecedents of the glass transition. In an effort to shed light on the crystallization behavior of some glass-formers, some have sought to establish a correlation between local mobility and a-relaxation parameters, most especially fragility. Local movements in glass are susceptible to processing and storage-induced changes in its spatial or dynamic heterogeneity, which may have negative impacts on the material. Therefore, although the global mobility of aged glass reduces, local movements may be augmented under the same circumstances. Systems using pharmaceuticals are especially susceptible to the effects of local movements in multicomponent systems. For instance, the local movements of a therapeutic protein in a lyophile may be dictated by the relative concentrations of excipients, which may have implications for the stability of the macromolecule. Certain interactions, like hydrogen bonding, are likely to affect local mobility. Therefore, local movements may be impacted by changes in hydrogen bonding patterns of an interest component as a result of interactions with other components in a molecule dispersion. The substantial progress achieved with nonpharmaceutical materials lays the

groundwork for future research into the properties of local mobility and its relationship to stability in medicines.

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