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RESEARCH PAPER

Molecular Motions in Sucrose-PVP and Sucrose-Sorbitol Dispersions—II. Implications of Annealing on Secondary Relaxations

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ABSTRACT

Purpose To determine the effect of annealing on the two secondary relaxations in amorphous sucrose and in sucrose solid dispersions.

Methods Sucrose was co-lyophilized with either PVP or sorbitol, annealed for different time periods and analyzed by dielectric spectroscopy.

Results In an earlier investigation, we had documented the effect of PVP and sorbitol on the primary and the two secondary relaxations in amorphous sucrose solid dispersions (1). Here we investigated the effect of annealing on local motions, both in amorphous sucrose and in the dispersions. The average relaxation time of the local motion (irrespective of origin) in sucrose, decreased upon annealing. However, the heterogeneity in relaxation time distribution as well as the dielectric strength decreased only for β_1- (the slower relaxation) but not for β_2-relaxations. The effect of annealing on β_2-relaxation times was neutralized by sorbitol while PVP negated the effect of annealing on both β_1- and β_2-relaxations.

Conclusions An increase in local mobility of sucrose brought about by annealing could be negated with an additive.

KEY WORDS annealing · dispersions · molecular motions · secondary relaxation · sucrose

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INTRODUCTION

Amorphous pharmaceuticals are typically processed and stored below their T_g. Thus preparation (e.g., lyophilization) and storage of amorphous pharmaceuticals result in aging effects. The terms aging and annealing have been used interchangeably in the literature to describe the same effect, i.e., relaxation occurring in the glassy state over time at a fixed sub-Tg temperature. Donth has attempted to distinguish between the two terms and has described *aging* as a naturally occurring unintentional effect resulting in relaxation (2). On the other hand, *annealing* is used to denote the same effect when it is carried out intentionally in order to achieve a desired objective. We will use the terms according to these definitions. The dependence of global mobility on thermal history, and hence on aging, and its pharmaceutical implications have been documented (3–5). Aging of a glassy matrix results in a decrease in volume (densification), enthalpy and entropy. This leads to a decrease in global mobility and an increase in the heterogeneity of cooperative motions (6). These kinetic effects of lowered molecular mobility result in pharmaceutically desired properties, e.g., decreased rate and extent of water sorption (3, 7) as well as decreased chemical instability (4, 5). Recently, there have been many reports correlating global molecular mobility to physical stability in amorphous state (1, 8, 9). If molecular mobility is the determinant of physical stability, aging would be expected to result in a glass more resistant to crystallization. However, aged amorphous samples have been reported to crystallize more readily than fresh glasses, an observation attributed to nucleation during aging (1).

Local mobility or secondary relaxations in non-pharmaceutical materials have also been shown to be influenced by thermal history. Generally, upon annealing, JG-relaxation times as well as their heterogeneity have been found to decrease (10–13). This counterintuitive observation has been attributed to the non-uniform collapse of "islands of

mobility" (13). As a result, the domains having longer relaxation times would be kinetically frozen, resulting in an overall narrowing of the distribution as well as their shift to shorter times. This observation is especially important in light of the potential role of local motions not only in the stability of amorphous pharmaceuticals but also as precursors to the global mobility. Evidence of nucleation in glassy indomethacin after storage for 147 days at a temperature substantially below Tg (T_g–55) was attributed to local motions (14). The calculated critical size of nucleus (above which nuclei are stable and spontaneous crystallization can occur) of crystalline indomethacin was less than the characteristic length of the cooperatively rearranging region indicating that local motions are sufficient to form the critical nuclei (15). On the other hand, the activation energy of β-relaxations was found to increase with annealing temperature suggesting progression of non-cooperative β-relaxations to the cooperative α-relaxations (16). Similar effects would be expected on increasing the annealing time at a fixed temperature. Thus aging effects on local mobility would be important given their potential role in the stability of amorphous materials or as precursor to the glass transition.

In an earlier study (1), we used dielectric spectroscopy to characterize local and global mobility in sucrose-polyvinylpyrrolidone (PVP) and sucrose-sorbitol solid dispersions. In these systems, the additive (PVP/sorbitol) concentration was low (2.5% w/w). Although these systems were characterized by virtually identical glass transition temperatures (T_g), there were pronounced differences in global mobility which correlated with the crystallization tendency of sucrose. The systems were characterized by two β- or secondary relaxations (local mobility) and the slower mobility was identified as the Johari-Goldstein (JG) relaxation. Both sorbitol and PVP acted as anti-plasticizers with respect to local motions.

The objective of this study was to examine the effect of annealing below Tg on local motions, in both sucrose and its solid dispersions. Based on the above discussions, we hypothesize that annealing below the glass transition temperature would influence both the secondary relaxation times and their distribution in amorphous sucrose. In addition, annealing is expected to have different effects on the two secondary relaxations in glassy sucrose. Based on our earlier finding that additives altered the local motions in unannealed sucrose-PVP and sucrose-sorbitol dispersions, we hypothesize that the annealing effects on location motions would also be influenced by the additives.

MATERIALS AND METHODS

Crystalline sucrose (Sigma, St. Louis, MO, USA), sorbitol (Sigma, St. Louis, MO, USA) and PVP-K90 (Plasdone K-90, ISP Technologies Inc., Wayne, NJ, USA) were used as obtained.

The experimental details were described in our earlier publication (1). We have repeated some of the critical details here.

Preparation of Amorphous Phases

Lyophilization of sucrose was carried out in a tray freeze-drier (Model UNITOP 400 L, Virtis, Gardiner, NY, USA) using the freeze-drying protocol described earlier (1). Sucrose was co-lyophilized with either sorbitol or PVP using the same protocol. The additive concentration in the final lyophile was 2.5% w/w.

Dielectric Relaxation Spectroscopy (DRS)

The sample (~400 mg) was packed tightly between two copper coated brass electrodes (20 mm diameter) enclosed by a PTFE spacer in a dielectric relaxation spectrometer (Novocontrol Alpha Analyzer, Novocontrol Technologies, Germany). The electrodes, in parallel plate configuration, were screwed securely to minimize air gaps and also to ensure intimate contact with the sample. The PTFE spacer (thickness—2.1 mm, area—59.69 mm^2 and capacity—0.518 pF) was used to minimize errors due to stray capacitance or edge effects. The samples were heated to the desired temperature at 20°C/min (Novotherm® temperature controller). The frequency ranged from 10^{-1} to 10^7 Hz and the time for each measurement was ~ 15 min. Annealing was carried out *in situ* and the isothermal dielectric profiles were obtained at 0, 2, 12, 20 and 32 h.

The relative permittivity and dielectric loss of fused quartz was determined at several temperatures and was in excellent agreement with the reported values. The samples were handled in a glove box under nitrogen purge (RH < 3% at RT). The water content, measured by KFT, was consistently < 0.5%. In selected samples, after the DES experiments, the water content and the glass transition temperature were determined by KFT and DSC respectively and were found to be unaltered. Selected samples were confirmed to be amorphous at the end of the experiment by X-ray diffractometry.

Analysis of Dielectric Relaxation Spectroscopy Data

We observed two secondary relaxations and the relaxation profiles considerably overlapped. Using WinFIT® software, two Havriliak-Negami functions (Eq. 1) were used to simultaneously fit the two β-relaxations:

$$\varepsilon^*(\omega) = \sum_{i=1}^{2}\left[\varepsilon_{\infty i} + \frac{\Delta\varepsilon_i}{\left(1+(i\omega\tau_i)^{\beta_i}\right)^{\gamma_i}}\right] + \frac{\sigma_0}{i\varepsilon_0\omega} \quad (1)$$

In Eq. (1), $\varepsilon^*(\omega)$ is the complex dielectric function consisting of the real part or dielectric permittivity, $\varepsilon'(\omega)$, and the imaginary part or dielectric loss, $\varepsilon''(\omega)$. ω represents the angular frequency which is equal to $2\pi f$ with f being the frequency in Hz. τ is the relaxation time and $\Delta\varepsilon$ is the dielectric strength or intensity given by $(\varepsilon_s - \varepsilon_\infty)$, where ε_0 is the vacuum permittivity and ε_∞ is the high frequency limit $(\omega\rightarrow\infty)$ of $\varepsilon'(\omega)$. β_{HN} is a parameter describing symmetric peak broadening with $0<\beta\leq 1$, γ_{HN} is the asymmetric broadening parameter with $0<\gamma\leq 1$ and σ_0 is the dc conductivity. The Havriliak-Negami equation has been used to fit broad and overlapping secondary relaxations in sucrose (17). One major drawback of dielectric spectroscopy, as observed with many sugars and polyalcohols, is the contribution of dc conductivity to the dielectric loss (18, 19). This can potentially interfere with the characterization of dielectric relaxation, if both occur in the same frequency region (18, 20). Equation 1 takes into consideration both relaxation and dc conductivity and was thus used to fit the dielectric spectra. Best fits were obtained with $\gamma_{HN}=0.8$ and the relaxation parameters τ, β_{HN} and $\Delta\varepsilon$ were obtained from the profiles at different temperatures.

RESULTS AND DISCUSSION

Baseline Characterization of the Amorphous Phases

The model systems used were sucrose (no additives) and sucrose co-lyophilized with either PVP or sorbitol (2.5% w/w additive). The glass transition temperatures of sucrose (no additives) and sucrose co-lyophilized with either PVP or sorbitol (2.5% w/w) were virtually identical (75 ± 1°C). Taking the T_g of sucrose to be 75°C, the Fox equation predicts T_g values of ~73 and ~77°C for molecular dispersions of sucrose with 2.5% w/w of sorbitol and PVP respectively. For sucrose-PVP mixture, since the free volume additivity does not hold, the experimental T_g values are typically lower (21) than those predicted assuming ideal mixing (e.g., Gordon-Taylor or Fox equation).

Effect of Annealing on Secondary Relaxation Times in Glassy Sucrose

Two secondary relaxations have been observed in several hydrogen-bonded systems (22, 23, 20, 24). The slower secondary relaxation was identified as the JG-relaxation while the faster one was attributed to specific interactions. Two secondary relaxations have also been reported in amorphous sucrose (17). These authors prepared amorphous sucrose by melt-quenching and identified the slower secondary relaxation as the Johari-Goldstein relaxation. The faster secondary relaxation was attributed to hydrogen bonding interactions or motion of the constituent glucose and fructose rings of sucrose. In agreement with the reported observation, in our studies, glassy sucrose exhibited two secondary relaxations (Fig. 1). For convenience, we designate the slower secondary relaxation as β_1 and the faster one as β_2. As is evident from the figure, the dielectric loss (and hence dielectric strength) of β_2- is larger than that of β_1- relaxation. Similar observations were made in sucrose and other hydrogen-bonded systems mentioned earlier.

Figure 2, an overlay of isothermal dielectric profiles of amorphous sucrose annealed for different times at 50°C, reveals the effect of annealing time. Similar isothermal experiments were conducted at other temperatures (40 and 60°C) well below the T_g (75°C). The two relaxations were simultaneously fitted to obtain the β_1- and β_2-relaxation times (Fig. 3, upper and lower panels). Under all the conditions, the β_1- and β_2-relaxation times decreased with annealing time. Thus the timescales of local motions, irrespective of their origin, were affected by annealing.

A decrease in JG-relaxation times upon annealing is expected. As has been explained for amorphous sorbitol, annealing results in non-uniform collapse whereby the slower domains contributing to the low frequency part of the JG-relaxation profile are kinetically frozen and contribute to the cooperative α-relaxations. However, the faster domains are minimally affected. Consequently, there is a narrowing of the relaxation profile and it shifts to higher frequency reflecting an overall decrease in JG-relaxation times as well as their distribution.

In our previous study, β_2-relaxations did not correlate with α-relaxations and this formed the basis for our conclusion that they are not the genuine JG-relaxations (1). In that case, the observed change in β_2-relaxation times upon annealing was counterintuitive. The answer is likely to lie in the molecular origin of the β_2-relaxations. While dielectric studies are not suited to provide insights into the precise origin of local motions, we can speculate based on discussions in the literature. Application of pressure decreased the number of hydrogen bonds in supercooled liquids resulting in an increase in mobility (25). It has also been postulated by the same authors

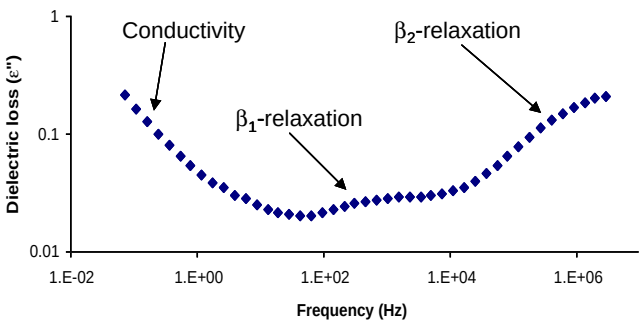

Fig. 1 Dielectric relaxation profile of amorphous sucrose at 50°C. Contributions of conductivity and β_1- and β_2-relaxtions to dielectric loss have been marked with arrows.

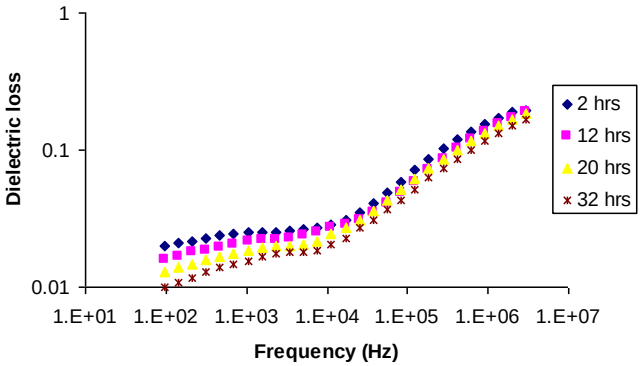

Fig. 2 Dielectric relaxation profiles of amorphous sucrose as a function of annealing time at 50°C.

that densification would cause a decrease in the number of accessible configurations of each molecule in the hydrogen bonded structure which would decrease the mobility. The net effect of these two processes would determine the observed change in relaxation properties. Densification brought about by annealing is expected to have a similar effect, albeit to a lower extent. The decrease in the β_2-relaxation times caused by annealing, reflect the more pronounced role of hydrogen bonding. Another possibility is that β_2-relaxation is a "pseudo-JG" relaxation as has been observed in some hydrogen bonded molecules, e.g., di- and tri-propylene glycol (23). In other words, β_2-relaxations may involve the motion of a considerable part of a molecule, sufficient to be affected by the non-uniform collapse of the "islands of mobility". As discussed below, the effects of annealing on other β_2-relaxation parameters (viz., β_{HN} and dielectric strength) were different from those on the corresponding β_1-relaxation parameters suggesting that β_2-relaxations are not the genuine JG-relaxations.

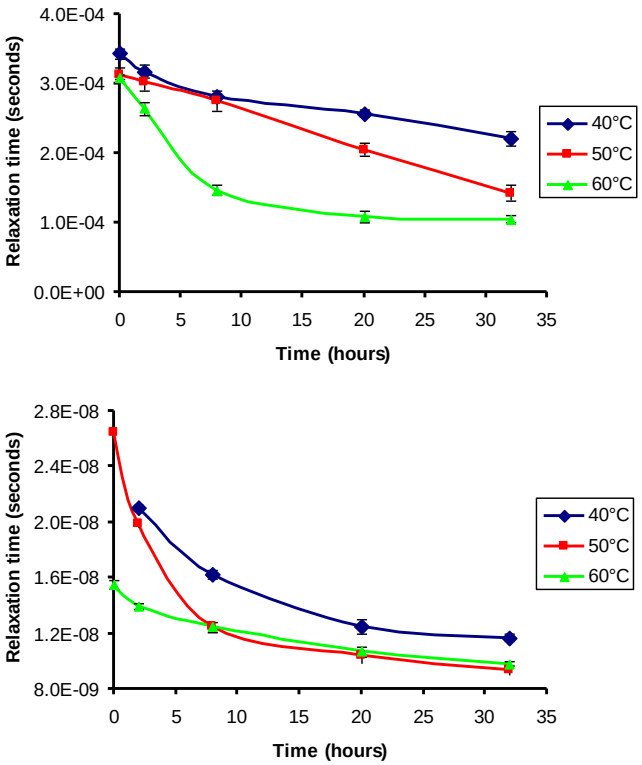

Fig. 3 The β_1- (*upper panel*) and β_2- (*lower panel*) relaxation times of amorphous sucrose as a function of annealing time. The annealing temperatures were 40, 50 and 60°C. Lines have been drawn to assist in visualizing trends. The β_2-relaxation time of the unannealed sample at 40°C ($6.1*10^{-8} \pm 1.6*10^{-10}$ s) was outside the scale of the y-axis and therefore could not be plotted.

The β_1-relaxation times continue to decrease after 20 h of annealing at 40 and 50°C but appear to have reached a "plateau" after annealing for 20 h at 60°C (Fig. 3, upper panel). The initial decrease in β_1-relaxation times, as a function of annealing time, is most pronounced at 60°C. As the annealing temperature approaches T_g (75°C), an acceleration is expected in the rate at which α-relaxations develop. It has been postulated that beta relaxation is a precursor to alpha relaxation (26). It is therefore not surprising that the annealing effect was the most pronounced at 60°C. In contrast, when annealed for a long time period, the β_2-relaxation times converged towards a value of $\sim 1*10^{-8}$ s irrespective of the annealing temperature.

Effect of Annealing on the Distribution of Secondary Relaxation Times in Glassy Sucrose

Figure 4 shows the distribution of β_1- (upper panel) and β_2- (lower panel) relaxation times as a function of annealing time. Since the peak broadening parameter, β_{HN}, of the Havriliak-Negami equation is inversely related to the peak width, the higher the value of β_{HN}, the lower is the heterogeneity in the distribution of relaxation times. As is evident from Fig. 4 (upper panel), the β_{HN} values of β_1-relaxations were virtually identical for the unannealed samples. In other words, the heterogeneity of distribution of β_1-relaxation times was not significantly influenced by the experimental temperature. At all temperatures, the heterogeneity in distribution of β_1-relaxation times decreased with annealing time (Fig. 4, upper panel). Annealing therefore leads to a more homogeneous JG relaxation. When annealed at 60°C, β_{HN} value appears to reach a plateau after 20 h of annealing. This is consistent with our earlier observation that the β_1-relaxation times had reached a plateau after 20 h of annealing (Fig. 3, upper panel). This observation also supports the argument that the decrease in relaxation times as well as the heterogeneity of relaxation time distribution are caused by collapse of the "islands of mobility".

Annealing had a negligible effect on distribution of β_2-relaxation times (Fig. 4, lower panel). Thus, although the β_2-relaxation times decreased upon annealing, there was no change in the heterogeneity of distribution. As discussed earlier, the decrease in relaxation times could be the result of a combination of breaking of hydrogen bonds and some

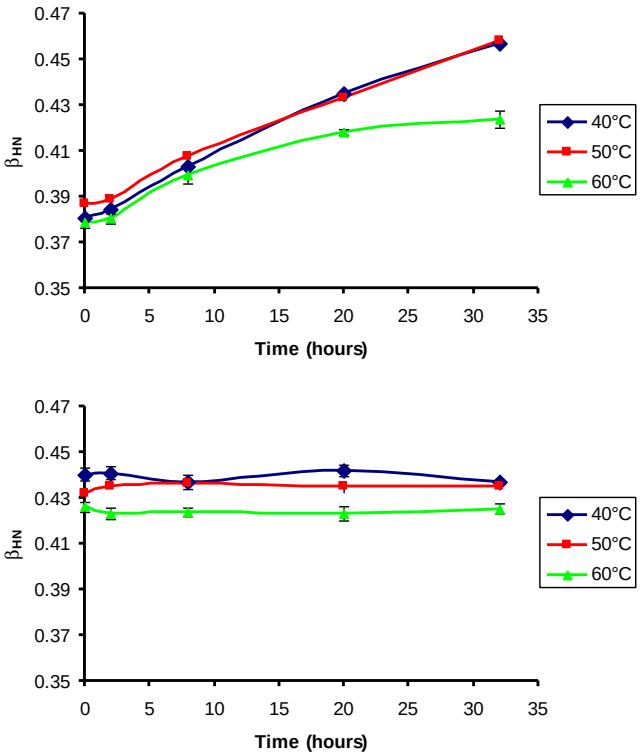

Fig. 4 The relaxation time distribution parameter, β_{KWW}, of β_1- (*upper panel*) and β_2- (*lower panel*) relaxation times of amorphous sucrose as a function of annealing time. The annealing temperatures were 40, 50 and 60°C. Lines have been drawn to assist in visualizing trends.

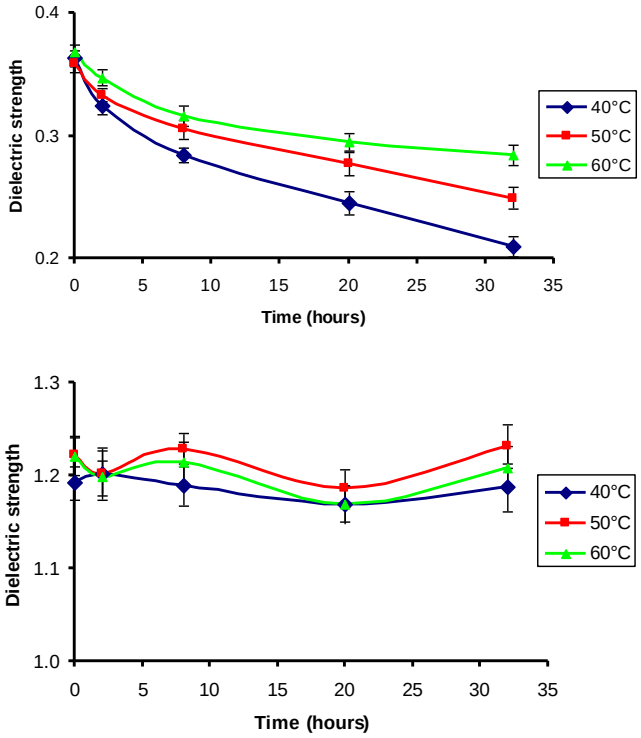

Fig. 5 The dielectric strength of β_1- (*upper panel*) and β_2- (*lower panel*) relaxations of amorphous sucrose as a function of annealing time. The annealing temperatures were 40, 50 and 60°C. Lines have been drawn to assist in visualizing trends.

dependence of β_2-relaxations on the volume of the system ("pseudo"-JG). The insignificant effect of annealing on β_2-relaxation time distribution points more towards their non-JG nature.

Effect of Annealing on the Dielectric Strength of Secondary Relaxations in Glassy Sucrose

Further insights into the two relaxations are obtained from the effect of annealing on dielectric strength (Fig. 5, upper and lower panels). Dielectric strength can be thought of as a measure of the number of dipoles participating in the dielectric relaxation process (27). The annealing-induced decrease in the dielectric strength of the JG-relaxations was attributed to a decrease in the number of relaxing dipoles resulting from the collapse of the low density regions (13, 28). Our results are in good agreement with this observation confirming that the β_1-relaxations are the JG-relaxations. On the other hand, annealing had a negligible influence on the dielectric strength of β_2-relaxations. This means that annealing induced collapse did not affect the number of dipoles participating in the β_2-relaxations. This would only be possible if the relaxations are due to motions of only parts of molecules and not the entire molecules as in JG-relaxations. Thus the idea that the β_2-relaxations might be the result of some specific interactions, e.g., hydrogen bonding, is supported by this observation.

To summarize, annealing resulted in faster local molecular motions irrespective of their origin. The effect of annealing time on change in distribution of relaxation times as well as dielectric strength was different for the β_1- and β_2-relaxations. The heterogeneity in relaxation time distribution and the dielectric strength of β_1-relaxations decreased upon annealing but there was no change in these properties of β_2-relaxations. In an amorphous pharmaceutical, aging during preparation or storage could result in a decrease in β_1-relaxation times as well as their heterogeneity, with potential implications on stability if the local motions are coupled to stability. As mentioned earlier, annealing of amorphous pharmaceuticals has been shown to improve chemical stability (4, 5). In these cases, chemical stability is expected to be coupled to global mobility. However, it is important to realize that the same strategy would not be successful in cases where stability is coupled to local mobility. This is because, as outlined above, annealing generally does not inhibit local motions.

Effect of Annealing on Secondary Relaxations in Sucrose Dispersions

Our next objective was to characterize the effect of annealing on local motions in sucrose dispersions. The primary reason for undertaking these studies was to examine the potential role of excipients to attenuate the increase in local motions brought

about by annealing. Annealing experiments were carried out in sucrose co-lyophilized with either PVP or sorbitol. The additive concentration was 2.5% w/w. Table I summarizes the effect of annealing on the β_1- and β_2-relaxation times at 40°C. In the sucrose-sorbitol system, only the β_1-relaxation times decreased as a function of annealing. The effect of annealing time was the same irrespective of the annealing temperature. The effect of annealing on β_2-relaxation times of sucrose was counteracted in presence of sorbitol. This is most likely due to a change in hydrogen bonding structure in the glassy matrix brought about by the presence of sorbitol.

PVP negated the effect of annealing on both β_1- and β_2-relaxation times. Again, hydrogen bonding is likely to play a role in modifying the local motions, especially β_2-relaxations. Sucrose and PVP are known to have strong hydrogen bonding interactions (29) which would be different from the hydrogen bonding network in sucrose alone. Another contributing factor to the absence of annealing effect in sucrose-PVP system could be the minimization of the collapse of loosely packed regions. Addition of a polymer to a small molecule would lower the free volume which in turn would decrease the number of the "islands of mobility". Thus the local motions, especially the JG-relaxations, would be minimally affected by annealing in the sucrose-PVP system.

Table I summarizes the effect of annealing time at 40°C on relaxation time distribution and dielectric strength of β_1- and β_2-relaxations in the model systems. The sucrose-sorbitol system behaved like glassy sucrose in terms of the effect of annealing on both β_1- and β_2-relaxation time distribution as well as dielectric strength. This is exactly what we would expect given the nature of the influence of sorbitol on the local motions in sucrose under annealing conditions. In other words, since annealing decreased β_1-relaxation times in sucrose and sucrose-sorbitol systems, the heterogeneity of β_1-relaxation time distribution as well as the dielectric strength also decreased in both the systems. On the other hand, sorbitol negated the effect of annealing on β_2-relaxation times and expectedly there was no change in the other properties of β_2-relaxation upon annealing. PVP again canceled the effect of annealing on relaxation time distribution as well as dielectric strength of both β_1- and β_2-relaxations attributable to the free volume effect as well as hydrogen bonding between sucrose and PVP. Similar observations were made at the annealing temperatures of 50 and 60°C. Therefore, addition of a polymer like PVP could be an important stabilization strategy for amorphous pharmaceuticals. In addition to its anti-plasticization effect on global mobility, the presence of PVP can counteract the effect of annealing on local motions. Thus, local motions are not expected to become faster with aging in these solid dispersions which could have significant pharmaceutical implications.

CONCLUSIONS

A decrease in global mobility upon aging has been exploited to improve the chemical stability of amorphous pharmaceuticals. On the other hand, aging could alter local motions in an amorphous pharmaceutical in a way potentially detrimental to its stability. In order to simulate aging effects, glassy sucrose was annealed below T_g and changes in the properties of the two β-relaxations were characterized by dielectric spectroscopy. Local motions in sucrose, irrespective of their origin, became faster upon annealing at the expense of α-relaxations. However, the heterogeneity in relaxation time distribution as well as the dielectric strength decreased for β_1- but not for β_2-relaxations. This suggested the resemblance of the β_1-relaxations to Johari-Goldstein relaxations. The influence of amorphous additives on sucrose local motions upon annealing was investigated. Effect of annealing on β_2-relaxation times was neutralized in sucrose-sorbitol system attributable to hydrogen bonding interactions. PVP negated the effect of annealing on both β_1- and β_2-relaxations. These findings could serve as a guide to stabilize amorphous pharmaceuticals if local motions are found to be coupled to stability.

Table I Effect of Annealing Time on Relaxation Times, β_{HN} and Dielectric Strength in Amorphous Sucrose and Sucrose Co-lyophilized with Sorbitol or PVP at 40°C. The Effects on β_1- and β_2-Relaxations were Investigated. ↓, ↔ and ↑ Indicate Respectively a Decrease, No Change and an Increase in Values of Various Relaxation Parameters with an Increase in Annealing Time. Similar Trends were Observed Following Annealing at 50 and 60°C

	Relaxation times		β_{HN}		Dielectric strength	
	β_1	β_2	β_1	β_2	β_1	β_2
Sucrose	↓	↓	↑	↔	↓	↔
Sucrose + 2.5% w/w Sorbitol	↓	↔	↑	↔	↓	↔
Sucrose + 2.5% w/w PVP	↔	↔	↔	↔	↔	↔

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