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Thermomechanical Properties of Amorphous Saccharides: Their Role in Enhancing Pharmaceutical Product Stability

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Introduction

The thermochemical and thermomechanical properties of, and slow relaxation processes within amorphous carbohydrate matrices have grown into topics of interest and considerable research activity. Following the pioneering studies by Levine and Slade (1993) the significance of glass transitions of anhydrous carbohydrates became to be recognised by the food processing industry, especially in the areas of intermediate and low moisture product development. More recently, interest in the formation and properties of amorphous carbohydrates has also spread to the pharmaceutical process industry, where such compounds find extensive use as stabilisers and processing aids in various types of dry dosage formulations (Ahlneck and Zografi, 1990).

It has thus become clear that metastable and thermodynamically unstable, supersaturated states are of great practical importance, especially for mixtures in which eutectic phase separation does not occur spontaneously within observable periods. The combination of conventional phase coexistence curves with glass transition/composition profiles and, possibly, crystal nucleation information, in single representations, has given rise to the description 'state diagram' (Franks, 1982). The state diagram thus aims to incorporate a time dimension into the conventional phase diagram, in the sense that both vitrification and nucleation phenomena are kinetic rate processes, functionally quite unrelated to equilibrium phase transitions.

Of particular practical interest are mixtures in which one or more components might be able to crystallise spontaneously in real time, either wholly or partially, whereas other, coexisting solute species form supersaturated solutions, leading eventually to vitreous states (solid solutions). Of such systems, the ternary mixtures water/sucrose/glycine and water/sucrose/NaCl have received most attention (Suzuki and Franks, 1993; Shalaev *et al.*, 1996), because they serve as models for the processing and drying of therapeutic preparations designed for injection and infusion, such as blood

Biotechnology and Genetic Engineering Reviews – Vol. 16, April 1999
0264–8725/99/16/281–292 $20.00 + $0.00 © Intercept Ltd, P.O. Box 716, Andover, Hampshire SP10 1YG, UK

coagulating factors and peptide hormones. Even the solid/liquid equilibrium phase diagrams are of a complex nature, displaying not only the three anhydrous crystalline phases, but also several crystal hydrates, with multiple peritectic points, as well as hydrated or anhydrous stoichiometric compounds, *e.g.* between sucrose and NaCl. The state diagrams contain, in addition, ternary glass transition/composition surfaces, bounded by the glass transition temperatures of the three pure components.

It is the purpose of this short review to highlight some salient physical and chemical features of concentrated mixtures containing lower oligosaccharides, with emphasis on their nonequilibrium properties.

The glass transition

A common feature of sugars and other polyhydroxy compounds (PHC) is their reluctance to crystallise from aqueous solutions during drying by freezing or evaporation. Eutectic phase separation within the period of observation is therefore rare. Instead, supersaturated solutions are formed which ultimately undergo a glass transition at a characteristic temperature T_g.

Figure 1 illustrates a typical state diagram for an aqueous carbohydrate solution (Franks, 1994). The systems of most practical interest cover the stippled area that lies beyond the domain bounded by the liquidus and solidus curves, specifically between the saturation solubility, denoted by S, and the glass transition profile. Thus, an unsaturated, dilute solution A can be dried by freezing to the (notional) eutectic T_e and beyond, or by evaporation to S and beyond. The system has to traverse the region of supersaturation and instability in order to reach the vitreous state of 'kinetic stability' at B. All indications are that physical and chemical processes can occur in the region of instability (and even in the vitreous state) that are quite unlike those conventionally described in text books on phase equilibria and chemical kinetics or in the literature devoted to 'solutions'.

As a generic group, PHCs fulfil the requirements of slow crystallisation and 'interesting' solution rheology and chemistry. As water is removed from their dilute

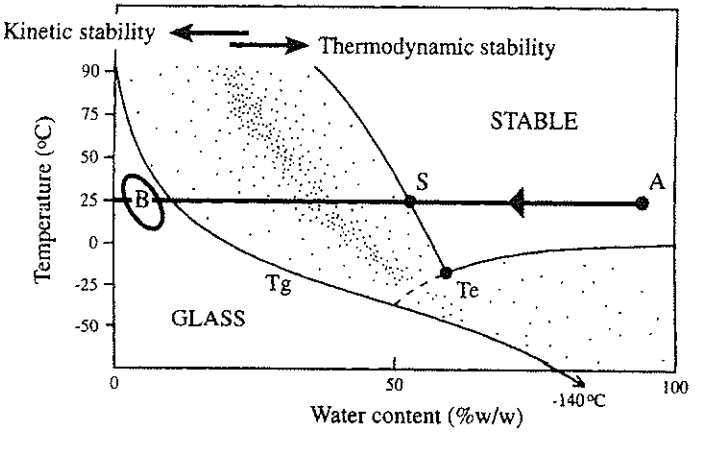

Figure 1. Regions of stability and instability (stippled) traversed during the drying of a dilute solution (A) to an amorphous glassy solid (B). The density of stippling corresponds to the degree of instability of the supersaturated solution. Reproduced, with permission, from Franks (1994).

Table 1. Glass temperatures of dry anhydrous PHCs; data from various sources

	T_g/°C
Glycerol	−93
Ribosde	−10
Xylose	−10
Sorbitol	−3
Mannitol	crystallises
Fructose	13
Glucose	39
Sucrose	70
Maltose.H_2O	70
Lactose	crystallises
Trehalose	106
Raffinose	109
Maltotriose	95
Stachyose	132
Destran[a]	84

[a]as supplied, without additional drying

solutions, either by freezing or by evaporation at ambient or elevated temperature, the viscosity of the supersaturated residue increases to the point, usually 10^{12}–10^{14} Pa s, where the mixture exhibits vitrification; it may then still contain up to 50% w/w of water, depending on the temperature at which the drying is carried out and the chemical nature of the solute(s).

The glass transition is usually determined by DSC; heating scans display a discontinuity in the heat flow (specific heat) at T_g. Angell (1995) has, however, pointed out that this heat flow discontinuity is not universally observed. This led him to differentiate between so-called strong and fragile fluids, depending on the intermolecular forces, where only members of the latter group, which contains hydrogen-bonded fluids, are expected to display DSC signals at T_g.

There remain large gaps in our understanding of the phenomenon of the glass transition, especially at the molecular level. Indeed, there does not yet exist a generally accepted theory for the origin of the glass transition. Some of the hypotheses that have been advanced from time to time cannot be tested experimentally, nor do they provide a measure of predictability. They are thus of very limited value to the technologist.

As a first approximation, T_g values of PHCs follow their molecular weights, as illustrated in *Table 1*. There are, however, some apparent anomalies. Mannitol, sorbitol, fructose, glucose and galactose are all monosaccharide hexoses displaying a considerable range of T_g values. Presumably, the molecular flexibility plays a role in determining the glass transition, although any relationship between molecular structure and glass 'structure' and T_g is still quite obscure.

Several empirical and semi-empirical relationships exist for the prediction of glass temperatures of single substances and of mixtures. For the group of PHCs it is found that the ratio $T_g/T_m \approx 0.7$ is a good predictor, where T_m is the melting point. For

Note added in proof: In a recent study of the behaviour shown by trehalose dihydrate during heating and drying, Sussich *et al.* (1998) found that the dried, amorphous sugar can be 'cold-crystallised' at 110°C to yield a new polymorph with a melting point in the neighbourhood of 215°C. This finding may have implications in the use of sugars as pharmaceutical excipients and makes a re-examination of the processes which accompany sugar dehydration and annealing highly desirable.

mixtures, T_g can be estimated in terms of the T_g values of the individual components and the mixture composition (Gordon and Taylor, 1952) with an acceptable degree of accuracy. Thus for a binary mixture,

$$T_g = \frac{wT_2 + k(1 - w)T_1}{w + k(1 - w)}$$

where w is the weight (or mol) fraction of solute (PHC) and T_1 and T_2 are the glass transition temperatures of components 1 and 2 (solute), respectively. The constant k is a fitting parameter which does, however, possess some physical significance. In practice, component 1 is usually residual water, where it acts as a ubiquitous plasticiser, i.e. it depresses the glass temperature of the mixture.

Experimental techniques

Of the various physical techniques by means of which slow processes in solids can be probed, thermoanalytical methods take pride of place. In particular, differential scanning calorimetry (DSC) has established itself as the method of choice by most workers. The study of vitrification, nucleation and crystallisation phenomena by temperature scanning methods (e.g. DSC) does however introduce complexities, because the measurements are often affected by the thermal history of the sample under study, so that the experimental procedures may need to rely for their reliability on well controlled annealing protocols and corrections for artefacts due to scanning rate, or change in sample configuration (collapse, powder coalescence) during the course of the measurement (Shalaev and Franks, 1995b). Care must be taken to ensure that the scanning rate does not exceed the rate of the process under observation.

Unfortunately, much of the published literature on aqueous solutions of PHCs is limited to the physical changes taking place in only one of the components, namely water, which may well be the major component of a mixture under study, but its behaviour also happens to be the least interesting aspect of the physical behaviour of such complex mixtures. This is particularly true for studies of physical and chemical changes during freeze-drying, because the ice formed during the initial freezing treatment is subsequently sublimed and plays no further part in any thermally induced changes of the 'product' phase. The advent of modulated DSC (MDSC) has facilitated the interpretation and deconvolution of superimposed reversible and/or irreversible processes, taking place at different rates, in complex mixtures (Izzard *et al.*, 1996). It is now possible to deconvolute complex cooling and heating scans and to obtain information on supercooling, crystal nucleation/growth during cooling and/or heating, eutectic crystallisation/melting behaviour and glass transitions, and thus to map ternary state diagrams.

The structures of crystalline solids are usually probed by X-ray diffraction techniques, and this has also been true for the elucidation of PHC crystal structures which tend to be of a complex nature. PHC molecules in the crystal are linked by hydrogen-bonds into infinite, three-dimensional, intermolecular networks, akin to the well-known structure of ice Ih.

For studies of related amorphous PHC states, X-ray methods have been of very limited use, although the rheological behaviour (high viscosity) of these substances in the fused state suggests that they are still extensively hydrogen bonded. Equally, the structural features of PHCs in solutions of hydrogen-bonding solvents remain to be

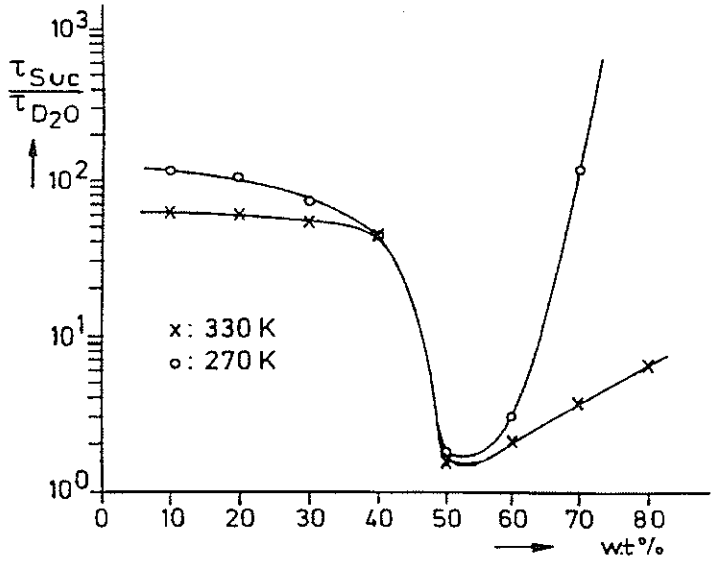

Figure 2. Rotational mobility of sucrose τ_{suc} relative to that of water τ_{D2O} as a function of the sucrose concentration. Redrawn, with changes, from Girlich (1991).

elucidated. In principle, neutron scattering, coupled with isotopic substitution, would appear to be a powerful method, but major experimental and data processing problems have so far prevented their exploitation. Recently, the first published neutron scattering study of glucose in the crystalline, fused and glassy state has highlighted the similarity between the close-range order in the crystal and the amorphous forms (Tromp *et al.*, 1997). Thus, the main differences relate to the heterogeneity in the hydrogen bonding details, i.e. bent hydrogen bonds in the amorphous states, but few changes in the number of hydrogen bonds per glucose molecule. Similarly, vitrification from the fused liquid state produces few *structural* changes in the intermolecular ensemble.

The conformations of PHCs in the presence of solvents capable of interacting by hydrogen bonding also requires further study. The permissibility of extrapolating from crystal structures to *structure* in solution was treated by Jeffrey (1973) who concluded that the PHC conformation observed in the crystal forms a valid starting point for calculations or simulations or as a close approximation to one or more possible rotamers which may exist in solution.

This thesis was subsequently tested on mannitol and sorbitol in aqueous and nonaqueous solvents, by a combination of ^{1}H n.m.r. and Molecular Dynamics simulation methods (Franks *et al.*, 1991). It was found that the nature of the solvent affected several of the torsional bond angles, and that some of the bond angles were identical to those found in the crystal, whereas others deviated significantly from the crystal geometry, giving the PHC molecule a distinctly different time-averaged conformation in solution. This may account for the observation that most PHCs do not crystallise easily from a saturated aqueous solution in real time.

The diffusional dynamics in aqueous PHC solutions have been probed by n.m.r. relaxation measurements (Girlich, 1991). *Figure 2* illustrates some of the surprising results for sucrose and water in their mixtures: the rotational motions of the two

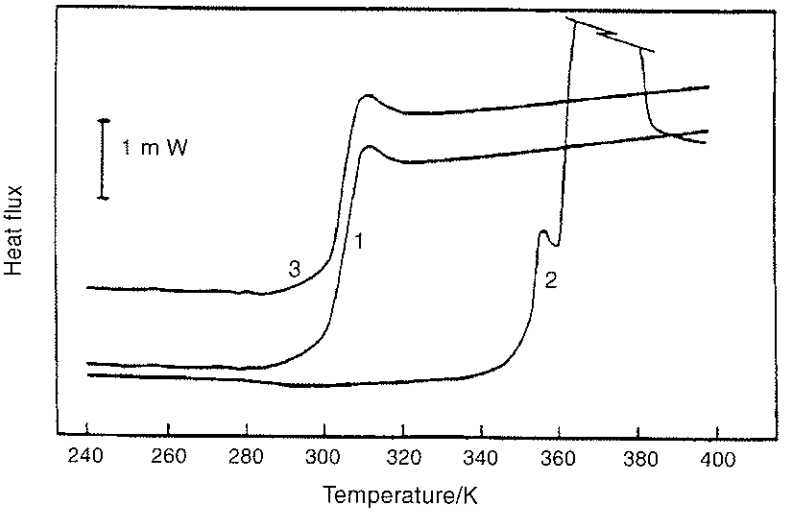

Figure 3. DSC heating scans of previously cooled amorphous trehalose, containing 8% residual water; 1: first heating scan; 2: heating scan after exposure at 82°C over-night; 3: scanned immediately after recording scan 2 and cooling to −33°C. Reproduced, with permission, from Aldous *et al.* (1995).

molecular species are uncoupled in dilute solution, as would be expected. With increasing concentration, the motions become strongly coupled. Finally, at high sucrose concentrations, as the glass transition is approached, the motions once again become decoupled. Even in the glass, water motions, down to −150°C, are characteristic of those found in liquid water, although the amorphous sugar matrix has all the properties normally associated with a solid. This remarkably high water mobility may be able to explain the influence of residual water in glasses on the chemical stability of substances encapsulated in excipient glasses.

The amorphisation and recrystallisation of PHCs

For PHCs to function as lyoprotectants in labile therapeutic preparations, the formulator should be aware of their physical properties, in particular of any changes that might occur in their physical state, either during processing or during long-term storage. If it is desired to produce an amorphous preparation, then inadvertent crystallisation is likely to cause severe deterioration in the biological activity of the labile product. On the other hand, the crystallisation of a hydrated PHC from the solid solution may be beneficial, because it removes water which might have migrated into the product to be stabilised.

Since amorphous states are thermodynamically unstable, the probability of crystallisation in real time of PHCs from supersaturated solution, from the melt, or from the amorphous solid cannot be discounted, provided that the appropriate physical conditions exist. In principle, this is equally true for the crystallisation of stoichiometric hydrates, given the required mol ratio sugar:water. Knowledge of the rates of such processes is then required for any predictions of long-term stability.

One may speculate that, above T_g, such rates are proportional to $(T - T_g)$. In preliminary studies of physical transformations in dried trehalose and raffinose

containing low amounts of residual water, Aldous *et al.* (1995) observed amorphisation and recrystallisation processes. This is illustrated for trehalose in *Figure 3*. Scan 1 shows the expected glass transition of trehalose, containing 8% water. The prolonged heat treatment at a temperature just below the melting point of crystalline trehalose $2H_2O$ is sufficient to promote partial crystallisation of the dihydrate, with the amorphous residue displaying a much increased T_g (scan 2). Once melted, the hydrate does not recrystallise during the time it takes to cool the melt and to rescan the temperature range to the original T_g of the preparation.

Where carbohydrates are used as stabilising excipients, say for proteins, their devitrification above T_g generally leads to rapid bioinactivation. This process has been described for a freeze-dried preparation of calcitonin gene-related protein (2%), stabilised with lactose (95%) and containing 3% residual moisture. When exposed to a temperature above T_g (40°C), the anhydrous sugar crystallised irruptively, leaving a residual amorphous phase, now consisting of 40% protein and 60% 'residual' moisture with a subzero glass temperature (Franks, 1992). This type of sugar devitrification is therefore highly damaging and must be avoided by storage well below T_g of the preparation. On the other hand, the crystallisation of a sugar hydrate provides additional desiccation, by removing water from the amorphous phase, thereby increasing T_g and the storage stability. The degree of such desiccation depends on the mol ratio sugar:water and would therefore be expected to increase as the number of mols of water per mol of sugar increases, i.e. in the order

$$(\alpha,\alpha\text{-trehalose, melibiose, melezitose}).2H_2O < \text{mannotriose}.3H_2O <$$

$$(\beta,\beta\text{-trehalose, stachyose})\ 4H_2O < \text{raffinose}.5H_2O$$

It thus appears that an exceptional dry state stabilising potential of some sugars depends on 1) their ability to crystallise from a highly supersaturated solution in the form of a hydrate and 2) a rate of crystallisation that is sufficiently high at room temperature to prevent the degradation of a labile bioproduct being co-dried in the sugar solution. If the above hypothesis is correct, then *iso*-trehalose (β,β-trehalose) should be greatly superior, since on an equal weight basis, it can remove twice the amount of water from the dried preparation. A study of the glass forming and crystallisation potential of *iso*-trehalose revealed, unexpectedly, that this sugar crystallises much more rapidly from a freezing aqueous solution than does the α,α-isomer (Roberts and Franks, 1996).

The trisaccharide raffinose pentahydrate provides a particularly interesting, although not unique, example of amorphous/crystalline transitions. Saleki-Gerhardt *et al.* (1995), who reported on the vacuum dehydration of the sugar, found that progressive reduction in the mol ratio raffinose:water led to a progressive amorphisation of the crystalline hydrate. On the other hand, when the anhydrous, amorphous sugar was exposed to water vapour, it progressively recrystallised, until X-ray diffraction measurements indicated a 100% conversion to the crystal. However, the water uptake at this stage corresponded to the formation of a tetrahydrate, rather than the pentahydrate.

In a more recent study, Kajiwara and Franks (1997) re-examined the phase behaviour of raffinose-water systems. A close study of their X-ray diffraction data at different degrees of drying, coupled with a detailed DSC study, suggested that a crystalline raffinose tetrahydrate does indeed exist, although the shifts in the atomic oxygen positions from those in the pentahydrate are of a minor nature. Distinct

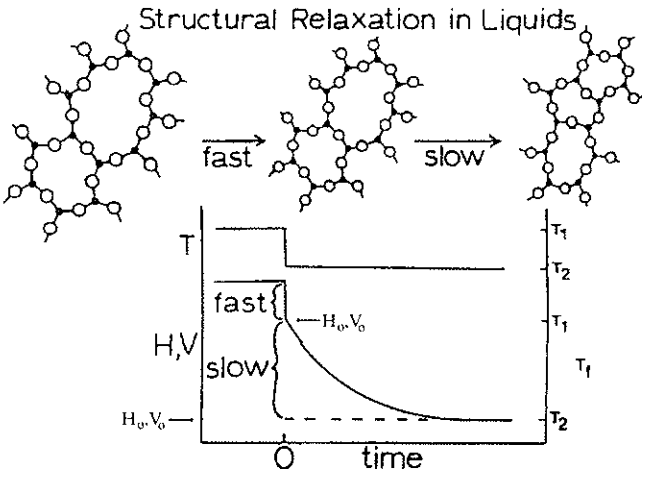

Figure 4. Schematic plot of enthalpy and volume against time during isothermal structural relaxation, following a step change in temperature. Adapted from Moynihan (1995).

melting points and enthalpies of fusion could, however, be identified. The phase diagram, although incomplete, also indicated a eutectic between the tetrahydrate and an even lower, as yet undefined, hydrate. As has also been reported for trehalose (Ding *et al.*, 1996), the (hypothetical) anhydrous crystalline state could not be produced in real time, despite various attempts at annealing and seeding. The rehydration and recrystallisation kinetics of the amorphised sugar show a complex dependence on the relative humidity which remains to be elucidated more thoroughly.

Dynamics and reactivity below the glass transition

Initial studies of PHC/water systems, used to stabilise labile biological substances and food products, e.g. enzymes, drugs, starch-based products, had led most investigators to the assumption that the glass transition provides a borderline between fairly rapid deterioration and complete stability (e.g. Slade and Levine, 1988; Green and Angell, 1989; Franks, 1990). It has become clear, however, that physical and chemical changes can, and do, take place within vitreous matrices, although not always at easily measurable rates.

An amorphous solid is characterised by a lack of a long-range, periodic order. It is an undercooled liquid which is thermodynamically unstable with respect to the crystal form. The energy barrier to viscous flow is high enough to prevent it from reverting to the stable, crystalline state within the normal time scale of observation. In a similar manner, other kinetic rate processes, e.g. chemical reactions, are severely inhibited in the glassy state. This makes the glass a valuable stabilising medium for labile materials.

For processes that are slow, relative to the time of observation, we need to consider the time evolution of equilibrium properties (H, V, structure, etc.). At equilibrium, the average structure is constant with time, but subject to fluctuations (dynamic equilibrium). Where fluctuations involve breaking and remaking of bonds and spatial

translation of molecules or groups of molecules, relaxation rates may become low (relative to the time of observation). A liquid can then be 'frozen' on the experimental time scale and take on the thermal and mechanical properties of a solid (on an appropriate time scale). All thermodynamic properties will then become (partially) time-dependent, i.e. they will exhibit an immediate response to a perturbation, followed by a slow approach to equilibrium (Moynihan, 1995). This is shown schematically in *Figure 4*. A step change in T or P in a melt produces crystal-like instant response (e.g. due to bond vibrations), followed by 'slow' structural relaxation (bond break/remake, hydrogen bonds in the case of carbohydrates?) until a new equilibrium is reached. The time decay can be expressed by a 'stretched exponential' and is characterised by a structural relaxation time τ.

Because of their complex hydrogen bonding topologies, saccharides exhibit such bond exchange properties to a high degree (e.g. syneresis and ageing of aqueous gels). Above T_g, the temperature dependence of τ is best expressed by the Vogel-Tammann-Fulcher (VTF) equation

$$\tau = A \exp[B/(T \quad C)].$$

where B and C are expressed as temperatures. The physical nature of C, as regards its description of PHC systems, is still under discussion. It used to be equated to T_g, but recent reports cast doubt on this interpretation. Below T_g, $\tau(T)$ exhibits Arrhenius kinetics, with high activation energies. For instance, the relaxation time for glycerol at its T_g (185K) = 33 min; at 170K, i.e. $(T_g - T)$ = 15K, the relaxation time is 4.5 days.

Temperature of zero mobility

The fact that neither physical nor chemical processes are completely inhibited in amorphous solids below T_g has given rise to a re-evaluation of dynamics in glassy matrices. Thus, below T_g, molecular relaxation times are too long for equilibrium to be established within an experimental timescale; this is related to a reduction in the number of accessible configurations (configurational entropy). The probability of a transition, W(T), is given by

$$W(T) = A \exp(-z\,\Delta U/kT)$$

where z is the number of molecules in a given domain, and ΔU is the potential energy barrier opposing the rearrangement. The critical size of the domain (z*) is related to the *configurational entropy* $S_c = Ns_c^*/S_c$. The critical configurational entropy s_c^* cannot decrease below k ln 2 (i.e. must have at least two configurations).

The average probability of a transition is given by A.exp(–const/TS_c). If the constant is *not* equal to zero, then we cannot attain the situation where $S_c = 0$ during a cooling process of finite time. Kauzmann (1948) first suggested that a temperature of 'zero mobility' T_o could be defined, such that, as $S_c \rightarrow 0$, so $T \rightarrow T_o$. Therefore $T_g \neq T_o$, but $T_g > T_o$ and the divergence increases with the magnitude of the constant, i.e. with ΔU. Thus, real glasses have a residual configurational entropy that increases with the difficulty of structural rearrangements. S_c can be obtained experimentally from calorimetric measurements. By putting ΔC = constant and $S_c(T_o) = 0$, then by integration, $S_c(T_g) = \Delta C \ln (T_g/T_o)$. It is found that for many 'real' materials, (e.g. oxides, silicates), $T_g/T_o = 1.29 \pm 11\%$.

From a semi-empirical treatment of relaxation processes it can be inferred that W(T) is proportional to τ^{-1}, and thus to diffusion and viscous flow.

If $[(T - T_o)/T_o] << 1$, then it can be shown that $W(T) = A.\exp[-B/(T - T_o)]$. This is the VTF equation (see above) which adequately describes diffusion and viscous flow, although not in the neighbourhood of T_g.

For multicomponent systems the situation is more complex, because the entropy of mixing must be included, and $\Delta S_{mix} > 0$. Complexities also arise with multicomponent systems made up of molecules of different sizes (and shapes?), e.g. sucrose + water, where decoupling of translational/ rotational motions are observed (Girlich, 1991). Experimental data are scarce. It is however firmly established that water remains mobile within a sucrose glass matrix. This finding may have important implications for chemical stability.

The fragility concept

Examination of reduced viscosity/temperature plots reveals a variety of behaviours. Some materials (SiO_2) display Arrhenius behaviour, i.e. ln (η/η_g) varies in a linear manner with T_g/T. For other materials the viscosity falls off much more steeply than is predicted by the Arrhenius equation.

Angell first advanced the 'fragility' concept: in so-called strong fluids, the structure (mainly covalent bonded) is maintained above T_g, whereas in fragile fluids, the structure is rapidly disrupted above T_g (labile hydrogen bonds?). According to this classification, PHCs and their (solid) aqueous solutions are fragile materials.

A fragility parameter δ is defined by

$$\delta = (\Delta U.s^*/k)/(T_g.\Delta C_{g\rightarrow l}), \text{ where } T_g/T_o = f(\delta)$$

The VTF equation can then be expressed in terms of the relaxation time, referred to T_o:

$$\tau = \tau_o \exp [\delta T_o/(T - T_o)]$$

Assuming that 17 orders of magnitude separate the relaxation times at T_g and at some common high temperature limit (the constant B in the VTF equation), then a linear relationship is obtained between T_g/T_o and δ:

$$T_g/T_o = 1 + 0.025\delta$$

Solving for δ, using some of the above equations and data from 'real' materials,

$$\delta = \frac{665}{(\Delta H^*/2.3RT_g) - 17}$$

Fragile liquids display VTF behaviour: δ is small, narrow glass transitions are observed, detectable by DSC. Strong liquids, on the other hand, display Arrhenius behaviour, with large δ values and broad glass transitions which are difficult to detect by DSC.

Implications for long-term physical/chemical stability

Physical stability is clearly related to viscosity, and hence, to structural relaxation. *Chemical* stability may be subject to additional factors, e.g. possibility of reactions triggered by intramolecular rearrangements. Parameters which describe stability include $\tau(T)$, T_o, δ, and $\eta(T)$. They can be obtained from scanning and isothermal calorimetry.

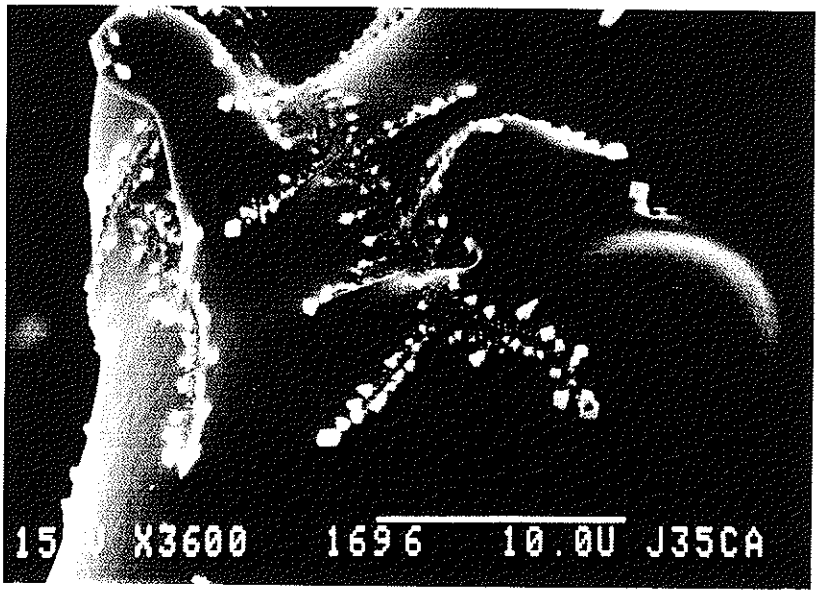

Figure 5. Scanning electron micrograph of freeze-dried sucrose/NaCl solution (mass ratio 5:1), containing 3% residual water and stored for several days at *ca.* 5 degrees below its T_g. The scale bar represents 10 μm.

The relationship between physical and chemical stability (if any) is not yet clear. According to Pikal (personal communication), the chemical stability of 'dry' human growth hormone, formulated with stachyose or trehalose, and measured as aggregation or chemical degradation at 40 and 50°C, is related to $(T-T_o)$, rather than $(T-T_g)$. Another recent report describes the kinetics of chemical bond cleavage reactions in materials held in a variety of amorphous PHC matrices, above and below T_g (Streefland *et al.*, 1998). It was found that the reactions were severely retarded, but not inhibited below T_g, and also that the PHCs with the highest glass temperatures (dextran) were less effective in retarding the reaction than simple disaccharides (sucrose) with lower T_g values.

The effect of slow relaxations on a physical transformation (phase separation) is graphically demonstrated in *Figure 5* which shows an electron micrograph, taken of a freeze-dried ternary solution (water/NaCl/sucrose) after several days storage just below its glass transition (Van den Berg *et al.*, 1993). Concurrent DSC had shown that during the initial freezing, NaCl did not crystallise, i.e. no eutectic phase separation was observed. After the sublimation of ice, the mixture was therefore completely amorphous. The micrograph reveals the slow crystallisation of well-formed cubic NaCl crystals at stress cracks in the amorphous matrix. At the time when the photograph was taken, the crystals had achieved approx. 0.1 μm dimensions. The growth rate would be expected to follow VTF kinetics.

Conclusions

Largely because of its involvement in governing the shelf life of labile pharmaceutical and food products, the thermomechanical behaviour of water-soluble amorphous solids at a fundamental level is now receiving renewed interest. Basically, these materials resemble 'real' materials, such as polymers, oxides and silicates, in their

mechanical properties, but they differ from these substances in their structural composition which relies on orientation-specific, hydrogen-bonded networks, rather than on covalent bonds.

It is becoming apparent that most theoretical approaches which have been developed for 'real' materials can also be applied to amorphous PHC-based materials, but experimental data are as yet scarce.

The relationships between thermomechanical attributes and chemical stability remain to be elucidated, as does also the role of residual water in preparations which are usually prepared by drying a dilute aqueous solution. The significance of the temperature of zero mobility as governing long-term stability remains to be demonstrated.

References

AHLNECK, C. AND ZOGRAFI, G. (1990). *International Journal of Pharmaceutics* **62**, 87.
ALDOUS, B.J., AUFFRET, A.D. AND FRANKS, F. (1995). *Cryo-Letters* **16**, 181.
ANGELL, C.A. (1995). *Science* **267**, 1924.
DING, S.-P., FAN, J.L., GREEN, L., LU, Q., SANCHEZ, E. AND ANGELL, C.A. (1996). *Journal of Thermal Analysis* **47**, 1391.
FRANKS, F. (1982). In *Water–A Comprehensive Treatise*, Vol. 7. Ed. F. Franks, Chapter 3. New York: Plenum Press.
FRANKS, F. (1990). *Cryo-Letters* **11**, 93.
FRANKS, F. (1992). *Japanese Journal of Freezing and Drying* **38**, 5.
FRANKS, F. (1994). *Bio/Technology* **12**, 253.
FRANKS, F., DADOK, J., YING, S., KAY, R.L. AND GRIGERA, J.R. (1991). *Journal of the Chemical Society, Faraday Transactions* **81**, 579.
GIRLICH, D. (1991). *Ph.D. Thesis*, University of Regensburg.
GORDON, M. AND TAYLOR, D.S. (1952). *Journal of Applied Chemistry* **2**, 493.
GREEN, J.L. AND ANGELL, C.A. (1989). *Journal of Phyical Chemistry* **93**, 2880.
IZZARD, M.J., ABLETT, S., LILLFORD, P.J., HILL, V.L. AND GROVES, I.F. (1996). *Journal of Thermal Analysis* **47**, 1407–1418.
JEFFREY, G.A. (1973). *Advances in Chemistry, Series Number* **117**, 177.
KAJIWARA, K. AND FRANKS, F. (1997). *Journal of the Chemical Society, Faraday Transactions* **93**, 1779.
MOYNIHAN, C.T. (1995). *Reviews in Mineralogy* **32**, 1.
ROBERTS, C.R. AND FRANKS, F. (1996). *Journal of the Chemical Society, Faraday Transactions* **92**, 1337.
SALEKI-GERHARDT, A., STOWELL, J.G., BYRN, S.R. AND ZOGRAFI, G. (1995). *Journal of Pharmaceutical Science* **84**, 318.
SHALAEV, E.YU. AND FRANKS, F. (1995a). *Thermochimica Acta* **255**, 49.
SHALAEV, E.YU. AND FRANKS, F. (1995b). *Journal of the Chemical Society, Faraday Transactions* **91**, 1511.
SHALAEV, E. YU., FRANKS, F. AND ECHLIN, P. (1996). *Journal of Physical Chemistry* **100**, 1144.
SLADE, L. AND LEVINE, H. (1988). *Pure and Applied Chemistry* **60**, 1841.
SLADE, L. AND LEVINE, H. (1993). In *The Glassy State in Foods*. Eds. J.M.V. Blanshard and P.J. Lillford, pp 35–102. Nottingham: Nottingham University Press.
STREEFLAND, L., AUFFRET, A.D. AND FRANKS, F. (1998). *Pharmaceutical Research* **15**, 843.
SUSSICH, F., URBANI, R., PRINCIVALLE, F. AND CESARO, A. (1998). *Journal of the American Chemical Society* **120**, 7893.
SUZUKI, T. AND FRANKS, F. (1993). *Journal of the Chemistry Society, Faraday Transactions* **89**, 3283.
TROMP, R.H., PARKER, R. AND RING, S.G. (1997). *Journal of Chemical Physics* **107**, 6038.
VAN DEN BERG, C., FRANKS, F. AND ECHLIN, P. (1993). In *The Glassy State in Foods*. Eds. J.M.V. Blanshard and P.J. Lillford, p 249. Nottingham: Nottingham University Press, Nottingham.