Glass-State Amorphous Salt Solids Formed by Freeze-Drying of Amines and Hydroxy Carboxylic Acids: Effect of Hydrogen-Bonding and Electrostatic Interactions

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We studied effect of molecular interactions on the physical properties of binary freeze-dried solids and frozen aqueous solutions using model chemicals containing various functional groups (amino, carboxyl, hydroxyl). Thermal analysis of frozen solutions containing alkyl diamines and hydroxy di- or tricarboxylic acids showed thermal transitions (T_g': glass transition of maximally freeze-concentrated phase) at temperatures higher than those of the individual solutes. A binary frozen solution containing 80 mM 1,3-diamino-2-hydroxypropane (single-solute $T_g' < -60$ °C) and 120 mM citric acid (single-solute T_g': −55.0 °C) made the transition at −30.8 °C. The molecular weight of the solutes had smaller effects on the transition temperatures of the frozen mixture component solutions. Lyophilization of some high T_g' mixture frozen solutions (*e.g.*, 1,3-diamino-2-hydroxypropane and citric acid) resulted in cake-structure amorphous solids with glass transition temperatures (T_g) higher than those of the individual components. Networking of intense hydrogen-bondings and electrostatic interactions between the heterogeneous molecules through the multiple functional groups was suggested to reduce the component mobility in the amorphous freeze-concentrated phase and the freeze-dried solids. Controlling the interactions should be a key to optimizing the physical properties of multi-component amorphous freeze-dried pharmaceutical formulations.

Key words freeze-drying; glass solid; thermal analysis; molecular interaction; salt

Glass-state amorphous solids are applied to pharmaceutical formulations as a way to improve dissolution of hydrophobic active ingredients (APIs) or to ensure stability of embedded biomacromolecules (*e.g.*, recombinant proteins) and drug delivery system (DDS) carriers (*e.g.*, liposome).[1—3] Freeze-drying is often a preferable method over other procedures (*e.g.*, quench-cooling of heat-melt solids) for the large-scale production of glass-state solid formulations containing thermally unstable ingredients. Dispersion of drug molecules into nonionic excipient matrices (*e.g.*, trehalose, polyvinylpyrrolidone (PVP)) is a popular way to make the non-crystalline formulations of many APIs that have intrinsic propensity for crystallization or low glass transition temperatures (T_g).[1] Insufficient miscibility with certain drug molecules and poor storage stability, however, often hinders the development of solid dispersion formulations using the nonionic matrices.

The application of salts or binary complexes is another approach to obtain stable amorphous solids.[4] For example, freeze-drying of sodium indomethacin results in an amorphous solid that has a glass transition temperature (120 °C) significantly higher than that of the free acid molecules (45 °C).[4,5] Recent studies indicated that the glass-state solids composed of excipient salts or salt-forming excipient combinations are promising as dispersion matrices.[6,7] Some pH-adjusting buffer salts (*e.g.*, monosodium citrate) form high T_g amorphous solids applicable to protein formulations.[7] Co-lyophilization of some basic amino acids (*e.g.*, L-arginine, L-lysine, L-histidine) with multivalent inorganic acids (*e.g.*, phosphoric acid) also results in the formation of protein-stabilizing glass-state solids.[6] High transition temperatures of the mixture freeze-dried solids suggest the contribution of strong intermolecular or inter-ion interactions to reducing the heterogeneous component mobility.

In contrast to the extensive studies on the physical properties and local structure of amorphous glass- or rubber-state solids composed of nonionic small molecules (*e.g.*, sucrose, sorbitol) or polymers (*e.g.*, PVP),[3] mechanisms that determine character of organic salts and/or heterogeneous components have not been well elucidated.[1,3] Recent intensive studies on ionic liquids (RTMS: room temperature molten salts) provided valuable information regarding the component ion structures, participating interactions, and the physical properties of the microscopically unordered non-crystalline salt systems.[8] Some earlier studies indicated feasibility to control the physical property of the amorphous salt solids by optimizing the component structure (*e.g.*, ion radius in indomethacin alkali metal salts)[4] and their compositions that determine the intermolecular and/or inter-ion interactions.

The purpose of this study was to elucidate the contribution of functional groups and the size of consisting molecules to the physical properties of multi-component frozen aqueous solutions and their freeze-dried solids. Thermal analysis of various combinations of model chemicals containing amino, carboxyl, and/or hydroxyl groups was performed to obtain the thermal transition temperatures (T_g, T_g': glass transition temperature of maximally freeze-concentrated phase) and propensity for crystallization in the frozen solutions and freeze-dried solids. Mid- and near-infrared analysis was performed to elucidate the molecular interaction in the freeze-dried solids. We also discuss the application of the amorphous mixture solids to pharmaceutical formulations.

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Experimental

Materials 1,3-Diaminopropane was purchased from Kanto Kagaku Kogyo Co. (Tokyo, Japan). 1,3-Diamino-2-hydroxypropane was the product of Sigma-Aldrich Inc. (St. Louis, MO, U.S.A.). Tricarballylic acid was obtained from Alfa Aesar GmbH & Co. KG (Karlsruhe, Germany). DL-Malic acid, D-(+)-malic acid, glycolic acid, L-(+)-tartaric acid, glutaric acid, adipic acid, DL-lactic acid (2-hydroxypropanoic acid), 1-aminopropane (propylamine), 1,4-diaminobutane, 1,6-diaminohexane, 1,8-diaminooctane, and other reagents were of analytical grade obtained from Wako Pure Chemical Industries Co. (Osaka, Japan).

Thermal Analysis Thermal analysis of frozen solutions and freeze-dried solids was conducted with a differential scanning calorimeter (DSC Q-10, TA Instruments, New Castle, DE, U.S.A.) with Universal Analysis 2000 software (TA Instruments). An aliquot (10 μl) of aqueous solution in an aluminum cell was cooled to −70 °C at 10 °C/min and then scanned at 5 °C/min. Freeze-dried solids (1—2 mg) in hermetic aluminum cells were scanned from −30 °C at 5 °C/min under nitrogen flow. Physical mixtures containing 1,3-diamino-2-hydroxypropane and citric acid (1.5—2.5 mg) in aluminum cells were melted at 165 °C for 3 min and then cooled rapidly by immersion in liquid nitrogen to prepare quench-cooled melt solids. The cells were transferred to the furnace of the calorimeter at 15 °C and then scanned from −50 °C at 5 °C/min to obtain the glass transition temperatures. Glass transition temperatures were determined as the maximum inflection point of the discontinuities in the heat flow curves.

Freeze-Drying A freeze-drier (Freezone-6, Labconco, Kansas City, MO, U.S.A.) equipped with temperature-controlling trays was used for lyophilization. Aqueous solutions containing the solutes (total 200 mM, 300 μl) in flat-bottom glass vials (13 mm diameter) were placed on the shelf of the freeze-drier at room temperature. The shelf was cooled to −40 °C at 0.5 °C/min and then maintained at that temperature for 2 h before drying. The frozen solutions were dried under vacuum (21 mTorr) maintaining the shelf temperature at −40 °C for 15 h, −30 °C for 6 h, and 35 °C for 6 h. The shelf was heated at 0.2 °C/min between the drying steps. The vials were closed with rubber stoppers under the vacuum. Solids for near-infrared analysis were prepared by freeze-drying the aqueous solutions (1 ml) in larger vials (18 mm diameter).

Mid- and Near-Infrared Spectroscopy (IR, NIR) An FT-IR spectrophotometer (MB104, ABB Bomen, Quebec, Canada) and GRAMS/32 software (Galactic Ind. Co., Salem, NH, U.S.A.) were used to obtain mid-infrared spectra of the solids (approx. 1 mg sample solid) in a pressed potassium bromide disk (approx. 250 mg). Transition spectra of the sample disks were obtained at 4 cm^{-1} resolution in 128 scans. Near-infrared spectroscopy was performed by using a Bruker MPA system with a diffuse-reflectance integrating-sphere probe (PbS detector) and OPUS software (Ettlingen, Germany). Near-infrared light was directed upward from the bottom of the glass vials containing freeze-dried solids to obtain the reflected signal over a range of 4000—12000 cm^{-1} with a resolution of 4 cm^{-1} in 128 scans.

Powder X-Ray Diffraction (XRD) and Residual Water Content Measurement The powder X-ray diffraction patterns were measured at room temperature with a Rint-Altima diffractometer (Rigaku, Tokyo, Japan) with Cu$K\alpha$ radiation at 40 kV/40 mA. The samples were scanned in the area of $5° < 2\theta < 35°$ at an angle speed of 5°/min. An AQV-6 volumetric titrator (Hiranuma Sangyo, Ibaraki, Japan) was used to determine the amount of water in the freeze-dried solids suspended in dehydrated methanol by the Karl–Fischer method.

Results

Figure 1 shows thermograms of frozen aqueous solutions containing a carboxylic acid and an amide (200 mM). The structure of the chemicals used in this study and their physical properties in the frozen solutions obtained by thermal analysis are summarized in Table 1. Some solutes showed intrinsic propensities to crystallize in the freeze-concentrated phases. An endotherm (−15.8 °C) in a frozen malonic acid solution suggested melting of the eutectic crystal. The exotherm (−53.1 °C) and endotherm (−19.3 °C) peaks

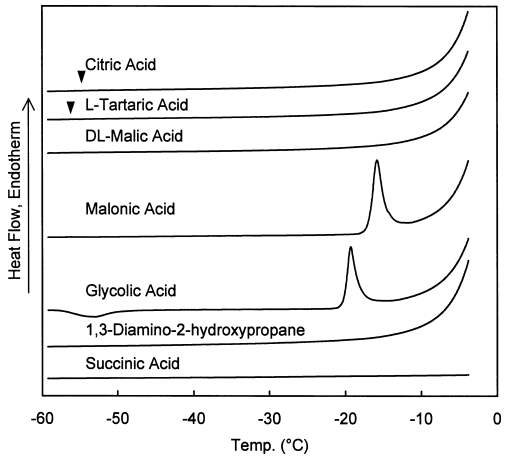

Fig. 1. Thermograms of Frozen Solutions Containing a Carboxylic Acid or an Amine (200 mM)

Aliquots (10 μl) of solutions in hermetic aluminum cells were scanned from −70 °C at 5 °C/min. Arrowheads denote the glass transition of maximally freeze-concentrated solutes (T_g').

Table 1. Structure and Thermal Property of Carboxylic Acids and Amines in Frozen Aqueous Solutions Obtained by Thermal Analysis

	MW	Functional groups			Property in frozen solutions	
		COOH	OH	NH_2	Crystallinity	Thermogram
Acetic acid	60.1	1	0	0	Crystallized	Endotherm
Glycolic acid	76.1	1	1	0	Crystallized	Exotherm/endotherm
DL-Lactic acid	90.1	1	1	0	Amorphous	$T_g' < -60$ °C
Malonic acid	104.1	2	0	0	Crystallized	Endotherm
Succinic acid	118.1	2	0	0	Crystallized	Flat
Glutaric acid	132.1	2	0	0	Crystallized	Flat
Adipic acid	146.1	2	0	0	Crystallized	Exotherm
Pimeric acid	160.2	2	0	0	Crystallized	Flat
L-Malic acid	134.1	2	1	0	Amorphous	$T_g' < -60$ °C
L-Tartaric acid	150.1	2	2	0	Amorphous	T_g': −57.1 °C
Tricarballylic acid	176.1	3	0	0	Amorphous	T_g': −52.1 °C
Citric acid	192.1	3	1	0	Amorphous	T_g': −55.1 °C
1-Aminopropane	59.1	0	0	1	Crystallized	Endotherm
3-Amino-1-propanol	75.1	0	1	1	Amorphous	$T_g' < -60$ °C
1,3-Diaminopropane	74.1	0	0	2	Amorphous	$T_g' < -60$ °C
1,4-Diaminobutane	88.2	0	0	2	Crystallized	Endotherm
1,6-Diaminohexane	116.2	0	0	2	Crystallized	Endotherm
1,8-Diaminooctane	144.3	0	0	2	Crystallized	Flat
1,3-Diamino-2-hydroxypropane	90.1	0	1	2	Amorphous	$T_g' < -60$ °C

observed in a heating scan of a frozen glycolic acid solution indicated eutectic crystallization and subsequent melting, respectively. The flat thermogram of a frozen succinic acid solution up to the ice-melting temperature suggested crystallized solutes. Some of these frozen solutions showed an exotherm that indicated eutectic crystallization in the cooling process before the thermal scan (data not shown). L-Tartaric acid and citric acid remained amorphous in the freeze-concentrated phase, presenting glass transition of the maximally freeze-concentrated solute phase (T_g') at $-55.1\,°C$ and $-57.1\,°C$, respectively.[7] The absence of particular thermal transitions and the gradual shift of the thermogram in some other single-solute frozen solutions (*e.g.*, DL-malic acid, 1,3-diamino-2-hydroxypropane) suggested that T_g' transition of the amorphous concentrated phase occurred at temperatures below the measurement temperature range ($<-60\,°C$).

Figures 2 and 3 show T_g' of frozen binary solutions containing various diamines and L-tartaric acid or citric acid. Most of the solute combinations showed a bell-shaped profile of T_g' that depended largely on the number of functional groups in the amines. Frozen mixture solutions containing amines and citric acid showed the T_g' peaks at lower acid molar ratios than in the combination with L-tartaric acid. Transition temperatures (T_g') of frozen solutions containing the acids and various diamines were significantly higher than those of the mixtures with monoamines (*e.g.*, 1-aminopropane). Slightly higher transition temperatures of the frozen solutions containing citric acid and 1,8-diaminooctane compared to those with smaller alkyldiamines (*e.g.*, 1,3-diaminopropane) indicated a relatively small effect of the component molecular size on the T_g' of the mixture phases. Introduction of hydroxyl groups to a diamine (*e.g.*, 1,3-diaminopropane to 1,3-diamino-2-hydroxypropane) raised the T_g' of the frozen mixture solutions to some extent. Mixing with L-tartaric acid or citric acid prevented crystallization of some amines (*e.g.*, 1,4-diaminobutane) in the frozen solutions. In contrast, some frozen mixture solutions showed thermal peaks that suggested crystallization of the salts. For example, a frozen solution containing 60 mM diaminooctane and 140 mM L-tartaric acid showed a T_g' ($-32.7\,°C$) and a eutectic crystallization exotherm peak ($-19.9\,°C$) in a thermal scan (data not shown).

Mixing of 1,3-diamino-2-hydroxypropane and some carboxylic acids (*e.g.*, succinic acid) also induced a significant upward shift of the T_g' (Fig. 4). The transition temperatures depended largely on the compositions of the carboxyl and hydroxyl groups in the acids. Most of the frozen mixture solutions showed the highest T_g' at the solute concentration ratios relatively rich in carboxylic acid. Alkyl chain length of the dicarboxylic acids gave limited effects on the T_g' of the mixture frozen solutions. DL-Malic acid and D-malic acid presented virtually identical T_g' profiles of the mixture frozen solutions. Mixing with 1,3-diamino-2-hydroxypropane prevented crystallization of some dicarboxylic acids (*e.g.*, malonic acid, pimeric acid) in the frozen solutions (data not shown). High T_g' of the frozen solutions containing 1,3-diamino-2-hydroxypropane and the hydroxy carboxylic acids (DL-malic acid, L-tartaric acid, citric acid) indicated a large effect of the hydroxyl group in reducing the component mobility in the freeze-concentrated phase. Frozen solutions containing 1,3-diamino-2-hydroxypropane and acetic acid or glycolic acid showed a gradual shift of the thermograms that suggested an amorphous mixture freeze-concentrated phase with T_g' below the measurement temperature range ($<-60\,°C$) (data not shown). The absence of apparent thermal transitions in frozen solutions containing some dicarboxylic

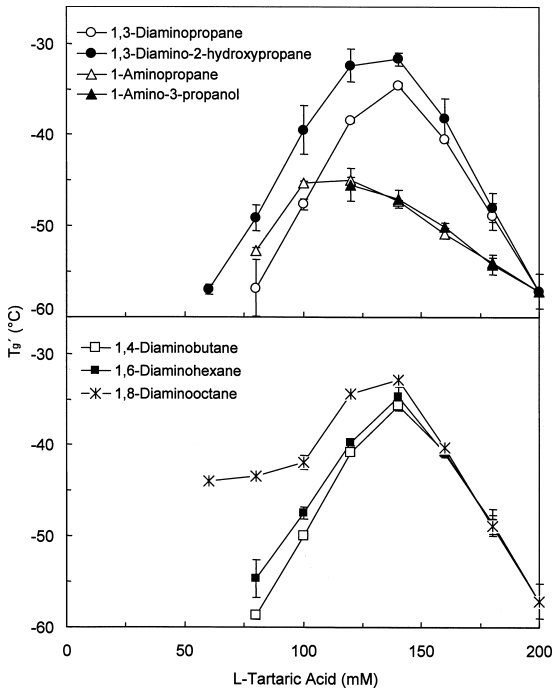

Fig. 2. Glass Transition Temperatures of the Maximally Freeze-Concentrated Phase (T_g') of Frozen Aqueous Solutions Containing L-Tartaric Acid and Various Amines

Frozen solutions (10 μl, 200 mM total) were scanned from $-70\,°C$ at 5 °C/min ($n=3$).

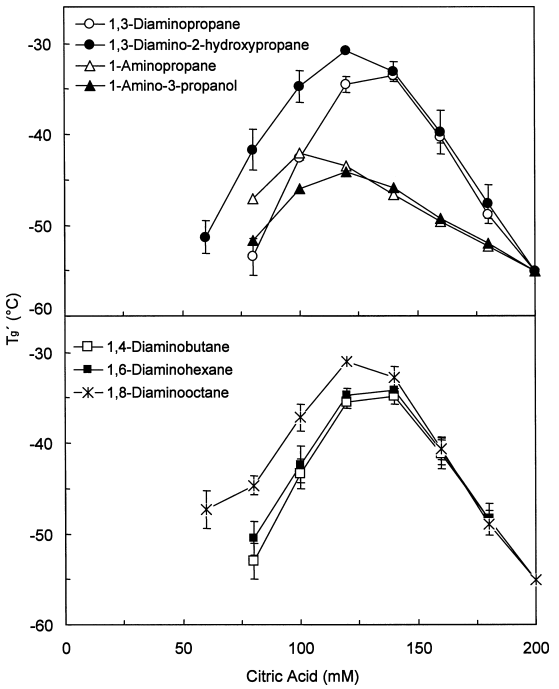

Fig. 3. Glass Transition Temperatures of the Maximally Freeze-Concentrated Phase (T_g') of Frozen Aqueous Solutions Containing Citric Acid and Various Amines

Frozen solutions (10 μl, 200 mM total) were scanned from $-70\,°C$ at 5 °C/min (average±S.D., $n=3$).

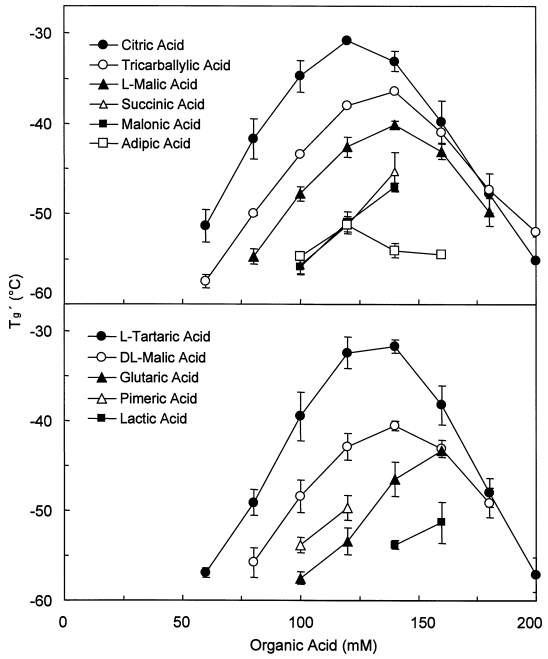

Fig. 4. Glass Transition Temperatures of the Maximally Freeze-Concentrated Phase (T_g') of Frozen Aqueous Solutions Containing 1,3-Diamino-2-hydroxypropane and Various Carboxylic Acids

Frozen solutions (10 μl, 200 mM total) were scanned from −70 °C at 5 °C/min (average±S.D., n=3).

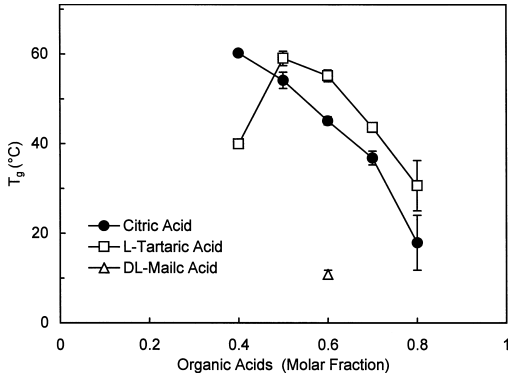

Fig. 5. Glass Transition Temperatures (T_g) of Freeze-Dried Solids Containing 1,3-Diamino-2-hydroxypropane and Organic Acids

The solids (1—2 mg) obtained by freeze-drying of aqueous solutions (200 mM total) were scanned from −30 °C at 5 °C/min (average±S.D., n=3).

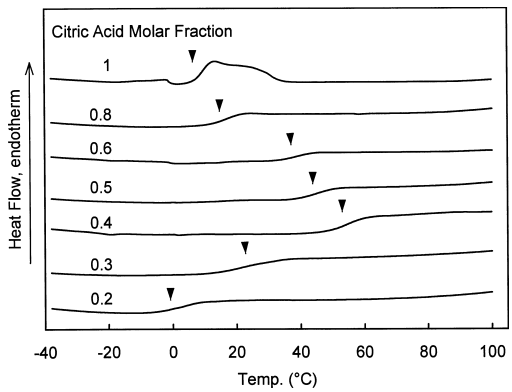

Fig. 6. Thermograms of Quench-Cooled Melt Mixture Solids Containing 1,3-Diamino-2-hydroxypropane and Citric Acid

The solids (1.5—2.5 mg) obtained by immersion of the heat-melt into liquid nitrogen were scanned from −30 °C at 5 °C/min.

acids (*e.g.*, succinic acid) and diamines (*e.g.*, diaminopropane) also suggested a large contribution of the hydroxyl groups to forming the high T_g' freeze-concentrated phase (data not shown).

Aqueous solutions containing 1,3-diamino-2-hydroxypropane and a hydroxy carboxylic acid (*e.g.*, DL-malic acid, L-tartaric acid, citric acid, 200 mM total) were freeze-dried to examine the physical properties of the resulting solids. The primary drying process at a shelf temperature (−40 °C) induced physical collapse in some lower T_g' (<−40 °C) samples, presumably because of the large molecular mobility of the freeze-concentrated phase.[9] Other frozen solutions were freeze-dried as cake-structure solids. Thermal analysis of the freeze-dried cake-structure mixture solids showed glass transitions (T_g) as high as 60.2 °C (Fig. 5, 120 mM 1,3-diamino-2-hydroxypropane, 80 mM citric acid). The solids freeze-dried from solutions containing 1,3-diamino-2-hydroxypropane and citric acid or L-tartaric acid at a 1 : 1 molar ratio showed amorphous components (halo patterns in the powder X-ray diffraction analysis) that have relatively high residual water (approx. 7—9%, w/w, data not shown). Amorphous solids of pure citric acid and 1,3-diamino-2-hydroxypropane were not available in the freeze-drying because of the physical collapse and crystallization that occurred during the process.

Quench-cooled heat-melt mixture solids containing 1,3-diamino-2-hydroxypropane and citric acid also showed a mixing-induced upward shift of the glass transition temperatures (Fig. 6). The highest transition temperature (54.5 °C) of the 0.4 citric acid molar fraction was slightly lower than that of the freeze-dried solid. Citric acid showed the glass transition of the quench-cooled solid at 9.5 °C.[10—12] The T_g of amorphous 1,3-diamino-2-hydroxypropane was not available using this method, and its low melting temperature (approx. 40—44 °C) strongly suggested a T_g below 0 °C (data not shown).

Mid-infrared analysis (FT-IR, KBr tablet transmission) of the amorphous mixture solids (0.5 citric acid molar fraction) prepared by freeze-drying and quench-cooling showed broad absorption bands (Fig. 7). Some relatively weak bands (*e.g.*, 1568 cm^{-1}) in the quench-cooled solid suggested evaporation of 1,3-diamino-2-hydroxypropane in the heating process. Non-destructive diffuse-reflection near-infrared (NIR) analysis of the freeze-dried mixture solids also showed broad bands typical for the amorphous solids (Fig. 8). Absence of some bands (*e.g.* N–H stretch 1st overtone of amino group at 6519 cm^{-1})[13] in the co-lyophilized solid (0.5 citric acid molar fraction) strongly suggested the interaction between the heterogeneous components that altered environment around the functional groups.

Discussion

Mixing of the alkyl diamines and hydroxy di- or tri-carboxylic acids induced high transition temperature amorphous concentrated phases in frozen aqueous solutions.[14] Some of the solute combinations formed cake-structure glass-state amorphous solids during freeze-drying. The high transition temperatures (T_g' and T_g) should allow faster drying processes at higher product temperature without physical collapse or shrinking of the solids.[9,15—17] Primary drying should

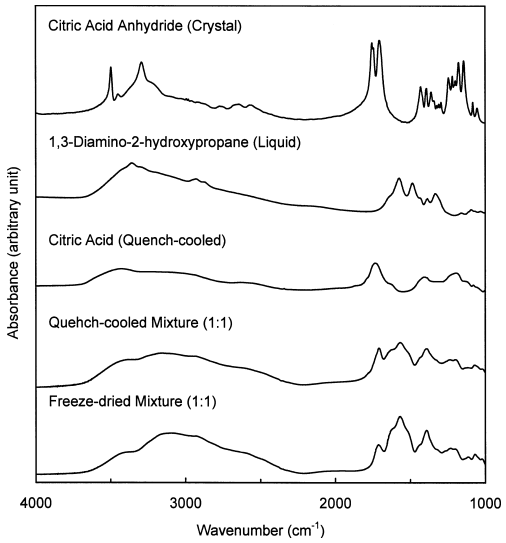

Fig. 7. FT-IR Spectra of Solids Containing 1,3-Diamino-2-hydroxypropane and Citric Acid

The mixture solids were obtained by quench-cooling of a melt (1 : 1 molar ratio, 165 °C, 3 min) or by freeze-drying of a solution (100 mM each).

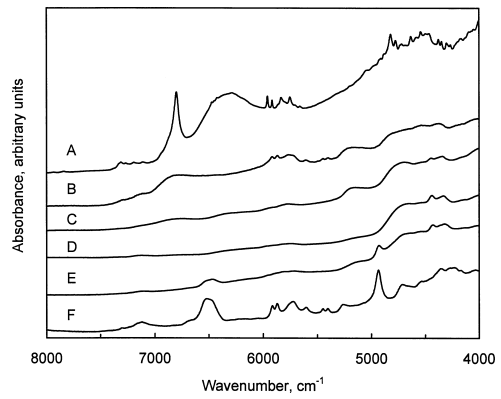

Fig. 8. Diffuse-Reflection Near-Infrared Spectra of Samples Containing 1,3-Diamino-2-hydroxypropane and Citric Acid

Each line denotes spectrum of anhydrous citric acid crystal powder (A), quench-cooled anhydrous citric acid melt (B), 1,3-diamino-2-hydroxypropane liquid (F), and solid lyophilized at the citric acid molar fraction of 0.3 (C), 0.5 (D), 0.7(E).

be conducted below the collapse temperature of the system (T_c), usually adjacent to and/or several degrees higher than the T_g', to obtain the pharmaceutically acceptable cake-structure solids. The primary drying is usually conducted at above −40 °C to accomplish ice sublimation on a practical timescale. Exposure of the partially dried solids above their glass transition temperature in the secondary drying process may shrink the cakes.

The bell-shaped profiles of the transition temperatures (T_g', T_g) depending on the component concentration ratio suggested strong attractive interaction between the components in the amorphous freeze-concentrated phase and the freeze-dried solids. Ideal mixing of nonionic molecules without particular attractive or repulsive interactions resulted in their glass transition at temperatures between those of the individual components, following the Gordon–Taylor equation.[11,18—20] It is also empirically known that frozen solutions containing the nonionic solute combinations have their thermal transition at temperatures (T_g') between those of individual solutes.[21,22] Significant upward deviation of the transition temperatures from those in the equation indicated the strong attractive interaction between the heterogeneous components. The mixing-induced transition temperature shift is also described as increasing "effective molecular weights" because many nonionic molecules (*e.g.*, polyols, saccharides) have the thermal transitions of the amorphous solids (T_g) or frozen solutions (T_g') at higher temperatures upon increasing the molecular weights.[23,24]

Networking of intense electrostatic interactions and hydrogen-bondings between the multiple functional groups should be a primary mechanism that raises the transition temperatures of the freeze-concentrated solute mixture phase and the freeze-dried solids.[4,6,25] The alkyl diamines and hydroxy di- or tri-carboxylic acids form ion pairs in aqueous solutions, and possibly in the freeze-concentrated phase. Some protonated polyamines selectively and strongly interact with particular dicarboxylates in aqueous solutions.[26] The ammonium carbohydrate ion pairs form multiple hydrogen-bonding in some non-polar solvents.[27,28] Continuous network of electrostatic interactions and hydrogen-bonding make the salt crystals popular supermolecular building blocks.[29] The differently protonated carboxyl and carboxylate groups also form an intermolecular hydrogen-bonding anion network.[30] It is plausible that the multi-component interactions contribute to the high transition temperature of the amorphous freeze-concentrated phase (T_g') and the freeze-dried solids (T_g). The eutectic crystallization observed in some high T_g' frozen solutions (*e.g.*, 60 mM diaminooctane and 140 mM L-tartaric acid) suggested effective interactions that induce the spatial ordering of the salt components above the transition temperature. Introduction of the hydroxyl groups to the components should provide additional hydrogen bonding in the amorphous phases. The limited effect of the component size on the transition temperatures also supported the significance of the interaction networks in determining physical properties.[23] Various factors, including the component structures, molar ratios, and water contents should alter the contribution of hydrogen-bonding and electrostatic (*e.g.*, ion–ion, ion–dipole, dipole–dipole) interactions in the amorphous phases. Further information on the interactions remains to be elucidated by other analytical methods (*e.g.*, solid-state NMR).

Recent studies on ionic liquids (RTMS: room temperature molten salt) also indicated the significant contribution of intermolecular (inter-ion) interactions to determining the physical properties of the locally disordered liquid or amorphous solid systems.[31,32] Factors that provide weak interaction between the molecules and/or ions (*e.g.*, size, charge distribution, functional groups) should induce low glass transition temperatures and low viscosities relevant to ionic liquids.[8] In contrast, glass-state solids would be designed by introducing strong interactions between the heterogeneous components.

The glass-state multi-component amorphous solids should be applicable in pharmaceutical formulations in several ways. Certain excipient mixture glass solids would become molecular dispersion matrixes that enable rapid dissolution of active ingredients or stabilization of biomacromolecules.[6] Some basic amino acids (*e.g.*, L-arginine) would be practical choices to form the glass-state mixture solids applicable in pharmaceutical formulations. The weakly acidic to alkaline pH of the high T_g mixtures and their re-hydrated solutions

would be preferable to ensure the storage stability of embedded molecules, as well as to reduce local stimulation in the site of parenteral application. Some pharmaceutically active ingredients (APIs) that have multiple amino or carboxyl groups may also form glass-state solids by direct interactions in mixing with some excipients.

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