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COMMUNICATIONS

The Effect of Thermal History on the Transition Temperature of Citric Acid Glass

Keyphrases □ Transition temperature—effect of thermal history, citric acid glass □ Citric acid glass—effect of thermal history on the transition temperature

To the Editor:

Glass is a noncrystalline solid which does not exhibit long-range order of its molecules and has a characteristic temperature where its physical state changes from a rigid, brittle material to a flexible, rubbery material. In addition, glass is not thermodynamically stable and will readily revert to the crystalline state under the proper environmental conditions (1, 2). As a result of these characteristics, materials capable of glass formation have been suggested as vehicles for solid dispersion systems, because it has been theorized that they should exhibit more rapid dissolution than their crystalline counterparts (3–5).

One compound often mentioned as a potential vehicle is citric acid (6–12). In the crystalline state, this material is highly hydrogen bonded (13), a property that apparently is responsible for its glass formation, because it has been reported that hydrogen bonding tendency helps prevent crystallization from occurring when a liquid melt is cooled below its liquidus temperature (14–16).

Recently, there has been a reported discrepancy in the transition temperature (T_g) of citric acid glass. This discrepancy was explained (17) to be due to residual moisture contamination in the samples. These studies (7–10) utilized citric acid monohydrate, while another study (12) employed anhydrous citric acid.

We do not dispute this explanation of the discrepancy. However, we thought it would be helpful to future investigators if the effect of thermal history of the melt and the presence of impurities on the T_g of citric acid glass was reported.

Anhydrous citric acid[1] was used in this study in order to eliminate possible effects of residual moisture contamination. The procedures used for sample preparation and determination of the T_g of a glass by differential scanning calorimetry (DSC) have already been discussed in detail (12). In examination of the effect of the thermal history of the molten citric acid on the T_g of citric acid glass, the DSC procedure was modified such that after heating the citric acid to melting, the molten citric acid was raised to the desired temperature and held isothermally for a specified time before rapidly being cooled.

Table I—The Transition Temperatures Obtained for Citric Acid Glass after Holding Molten Citric Acid Isothermally above Its Melting Temperature for Specified Times

Temperature°	Time, min	T_g Values°
172	5	10.0[a]
	15	7.0
	30	2.0
177	5	10.0
	20	4.0
180	5	8.0
	15	3.0
	30	0.0
190	5	6.5
	15	1.0
	30	—[b]

[a] Average of at least duplicate determinations. [b] Material discolored, not able to detect a T_g from −60 to 200°.

Table I shows the effect of thermal history on the T_g of citric acid glass. Results indicate that the higher the temperature and the longer the exposure time at a given temperature, the lower the T_g value of citric acid glass. Accompanying this decrease in the T_g value was a progressive discoloration of the molten citric acid from a clear transparent liquid to a yellowish brown liquid.

Aconitic acid[2], a dehydration decomposition product of citric acid, degrades upon melting. By adding the material to citric acid in varying proportions and then preparing glass dispersions of the mixture, it is possible to simulate the effect of degradation product impurities on the T_g of citric acid glass. Figure 1 shows that as the level of impurities increases, the T_g of citric acid glass decreases.

The thermal stability of citric acid has been of concern to previous solid dispersion investigators (6–10, 12). Available thermal analysis literature on citric acid is limited. One study (18) suggests that citric acid may begin to decompose at ~185°, while another study (19) states that thermal degradation of citric acid does not begin to occur until 200–225°. The data presented in this communication indicate that citric acid does exhibit some degree of thermal instability. However, thermal degradation does not appear to begin immediately upon initial melting but only

[1] J. T. Baker Chemical Co., Phillipsburg, N.J.

[2] Aldrich Chemical Co., Milwaukee, Wis.

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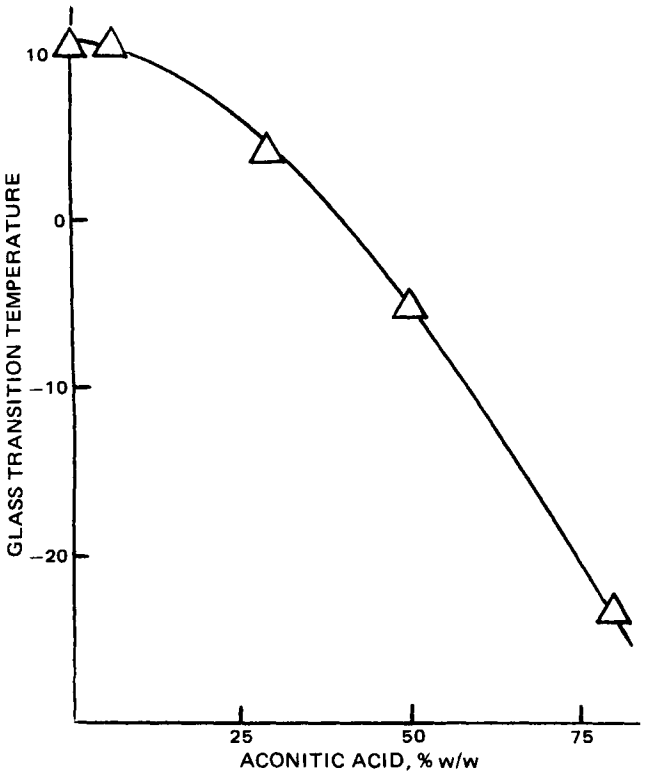

Figure 1—*The effect of aconitic acid on the transition temperature of citric acid glass.*

on prolonged exposure of molten citric acid to temperatures above its melting temperature. It has been shown previously that the sample preparation techniques used in this study did not adversely affect citric acid (12). In addition, the data also imply that low levels of impurities (<5% w/w) cannot be readily detected by DSC.

In preparation of citric acid glass, care should be taken to use the minimum amount of heat necessary to melt the citric acid, to avoid prolonged heating at temperatures of its melting point, and to employ a procedure in which there is some means of temperature control. Although these suggestions for the preparation of citric acid glass may make this material unsuitable for use in the commercial preparation of solid dispersion systems, it should not eliminate the use of this glassy vehicle as a tool for the examination of the compatability, miscibility, and stabilization of the glassy states of materials.

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Dose-Dependent Decrease in Heparin Elimination

Keyphrases □ Heparin—dose-dependent pharmacokinetics □ Pharmacokinetics—dose-dependent decrease in heparin elimination

To the Editor:

Studies on the pharmacokinetics of heparin have revealed dose-dependent (1–4), time-dependent (5), and assay-dependent (4) characteristics. The mechanisms underlying these characteristics are unknown but are likely to reside in the heterogeneity of heparin. Heparin is a natural mammalian glycosaminoglycan consisting of polymeric constituents arranged linearly, with different chain length and chemical composition and with a molecular weight ranging from 3000 to 45,000 (6–8). Recent studies have demonstrated that the antithrombin-III binding site of heparin, which is necessary for its pharmacological action, appears to reside in an oligosaccharide segment of the molecule that has a specific sequence of four to eight monosaccharides, *i.e.*, iduronic and glucuronic acids and glucosamines, with *N*-sulfate, *O*-sulfate, and *N*-acetyl groups being required at specific sites (9–11). The metabolism of heparin is not well understood. Although the metabolic processes involved are thought to include depolymerization and desulfation, the relationship between different metabolic processes and the decline in anticoagulant activity is unclear.

The biologic half-life of heparin increases with increasing dose in humans and animals (1–4). This dose-dependence is without any indication of Michaelis-Menten type kinetic characteristics (3, 4) and recently has been demonstrated in humans to be due to a dose-dependent decrease in the total clearance of the anticoagulant (4). The total clearance of heparin in humans usually is reported to be between 0.5 and 2 ml/min/kg, while the apparent volume of distribution is usually reported to be between 40 and 100 ml/kg (2, 4, 12–14). However, reported values for both of these pharmacokinetic parameters vary widely

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