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# THERMAL ANALYSIS STUDIES OF GLASS DISPERSION SYSTEMS

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## ABSTRACT

Glass dispersion systems were examined using differential scanning calorimetry. The addition of a crystalline additive to a glassy vehicle resulted in a reduction of the vehicle's glass transition temperature. Mixtures of glassy materials were immiscible, partially miscible, or completely miscible. The results can be explained using the concept of miscibility among liquids. By combining two miscible glasses in the proper ratio, it was possible to obtain greater physical stability than with either of its glassy components. This was demonstrated with a 1:1 mixture of citric acid and acetaminophen which showed no changes in its thermogram after seven weeks of storage at 23°C. The glass transition of this mixture is about 18°C.

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## INTRODUCTION

A solid dispersion concept often discussed in reviews (1-3) of this subject is the potential for glass forming materials as vehicles. Several recent publications have dealt with sugar type materials. Dextrose glass as a vehicle for solid dispersions was demonstrated with sulfabenzamide (4). Allen and co-workers (5) extended the application of sugars to corticosteroids. To overcome handling difficulties with these materials, the use of sugar and sugar derivative glassy vehicles was investigated (6). Sugars and their derivatives were also examined in dispersions with sulfamethoxazole (7).

Glassy citric acid as a potential vehicle for solid dispersion systems has been examined in detail by several investigators. Chiou and Riegelman (8) initially studied it in mixtures with griseofulvin. In a previous communication (9), we examined the glass formation of citric acid and the type of systems it formed with benzoic acid and phenobarbital. In addition, Summers and Enever have examined it alone (10) and in combination with primidone (11-13). Summers studied it in dispersions with barbiturates (14). Its use in dispersions with sulfabenzamide (4) has also been investigated.

Herein is described the results of a study which examined several types of glass forming systems when

mixing glass forming and non-glass forming materials.

## EXPERIMENTAL

### Materials:

One lot of each material was used in this study. The materials were not subjected to any purification procedures or stored in any special way unless specifically indicated.

The materials examined included acetaminophen[1], amobarbital[2], anhydrous citric acid[3], anhydrous dextrose[4], benzoic acid[5], hexobarbital[6], pentobarbital[7], phenobarbital[8], salicylamide[9], salicylic acid[10], sorbitol[11], sulfanilamide[12], and sulfathiazole[13].

### Methods:

Thermal Analysis: A differential scanning calorimeter[14] was used to determine the various transition temperatures and physical stability of the samples. The procedures were essentially identical to those described previously (9). Observed temperature values were corrected for chromel alumel thermocouples over a temperature range of -60°C to 400°C. Indium[15] was used as the standard. Neoprene[16], tin[17], and zinc[18] were also used to ensure that the temperature scale was accurate. Most determinations were made at least in duplicate. A 10°C/minute heating rate was used for all determinations unless otherwise specified. A 10-15 mg sample size

was necessary to obtain reproducible and distinct transition temperatures.

Sample Preparation: Two procedures were used for sample preparation, an in situ method and a bulk procedure. In the in situ method, pure material or a physical mixture of two materials in the desired ratio was accurately weighed directly into an aluminum sample pan[19]. An aluminum cover[20] was placed on the sample, and the pan transferred to the sample pan holder of the instrument. After heating the sample to melting, the melt was cooled to approximately -60°C by flooding the sample holder of the instrument with liquid nitrogen vapor (the cooling rate was about 60-70°C/min). The solidified melt was then reheated, and the thermogram recorded.

Bulk glass system preparation involved melting about 50 g of pure material or a mixture of two materials in the desired ratio in a electric frying pan[21] heated about 5°C higher than the melting temperature of the material(s). The melt was rapidly solidified by transferring it to an aluminum foil boat[22] located an a dry ice block. After solidification, the melt was removed from the dry ice and placed in a desiccator[23] over silica gel[24] at 23°C ± 1°C for 24 hr. The solidified melt was pulverized in a rotary granulator[25].

Samples of solidified melts prepared by the bulk procedure were stored in amber glass bottles with screw

caps[26] placed in desiccators over silica gel at 23°C ± 1°C and 37°C ± 1°C. Thermograms were run periodically to examine the effect of aging on their physical stability.

## RESULTS AND DISCUSSION

### Glass Formation:

A variety of compounds was examined in this study. They can be divided into two categories. Those found capable of glass formation and those that could not be put into the glassy state with the techniques used in this study. Table I lists the materials which were found capable of glass formation.

Glass is generally prepared by rapid quenching of a liquid melt (21). At the present time, there does not appear to be a comprehensive theory as to why some organic molecules can be easily put into the glassy state while others cannot. Kauzmann (22) stated that glass formation is probably a general property of the liquid state of matter. Others (14,23) could not find correlations between thermodynamic properties and glass formation tendencies in materials. Studies on metallic glasses (24) indicate that the main requirement for putting a material into the glassy state is to avoid the thermodynamically preferred crystallization process. It appears that most liquids can be made to solidify to a glass if they are cooled through the

TABLE I

Melting (Tm) and Glass Transition (Tg) Temperatures of the Compounds Found to Form Glasses

| Compound | Tm, °C | Tg, °C[a] | $\frac{Tg, °K}{Tm, °K}$ | Tg lit, °C (ref.) |
|---|---|---|---|---|
| Acetaminophen | 174.0 | 22.0 | 0.66 | |
| Amobarbital | 159.0 | 12.5 | 0.66 | -4 (14) |
| Citric Acid | 159.0 | 10.2[b] | 0.72 | 9 (10), -23 (12-14) |
| Dextrose | 159.0 | 37.4 | 0.72 | 25 (15), 40 (16), 27 (17), 7-27 (18), 5-15 (19), 38 (20) |
| Hexobarbital | 150.0 | 12.7 | 0.68 | 9 (14) |
| Pentobarbital | 135.0 | 6.3 | 0.69 | 4 (14) |
| Phenobarbital | 179.0 | 41.9[b] | 0.70 | 40.5 (14) |
| Sorbitol | 94.0 | -2.0 | 0.74 | |
| Sulfathiazole | 209.0 | 60.0 | 0.69 | |

[a] determined using *in situ* procedure

[b] previously reported by R.J. Timko and N.G. Lordi, J. Pharm. Sci., 68, 601 (1979)

crystallization temperature range more rapidly than the time required for crystal nuclei to form (25). This can be easily accomplished if the symmetry of the molecule is of low order, or the rotational isomerization from the equilibrium rotamer distribution to that re-

quired for crystallization is low at temperatures equal to or below the melting point. A high melt viscosity at or below the melting point along with the ability to hydrogen bond and steric considerations of the molecule may aid in the vitrification process (18,25,26).

The temperature at which a glass begins to soften when heated is generally referred to as the glass transition temperature (Tg) (27). Usually the thermodynamic properties of a glass such as specific volume, specific heat, viscosity, compressibility, and thermal conductivity all show changes around this temperature (18,21,24-28). Prediction of the transition temperature of a glass is difficult and risky. However, experimental data for a wide variety of semi-crystalline polymers indicate that the ratio of the glass transition temperature to the melting temperature (Tm) generally falls between 0.50 and 0.75 if the temperatures are compared in degrees Kelvin (29). For the materials listed in Table I, the ratio of Tg/Tm falls within this range.

Glass Dispersion Systems:

There are several possibilities when dealing with combinations of potential glass forming materials: (a) both materials form glasses, (b) one of the materials forms a glass while the other does not, and (c) neither material forms a glass. This study did not investigate

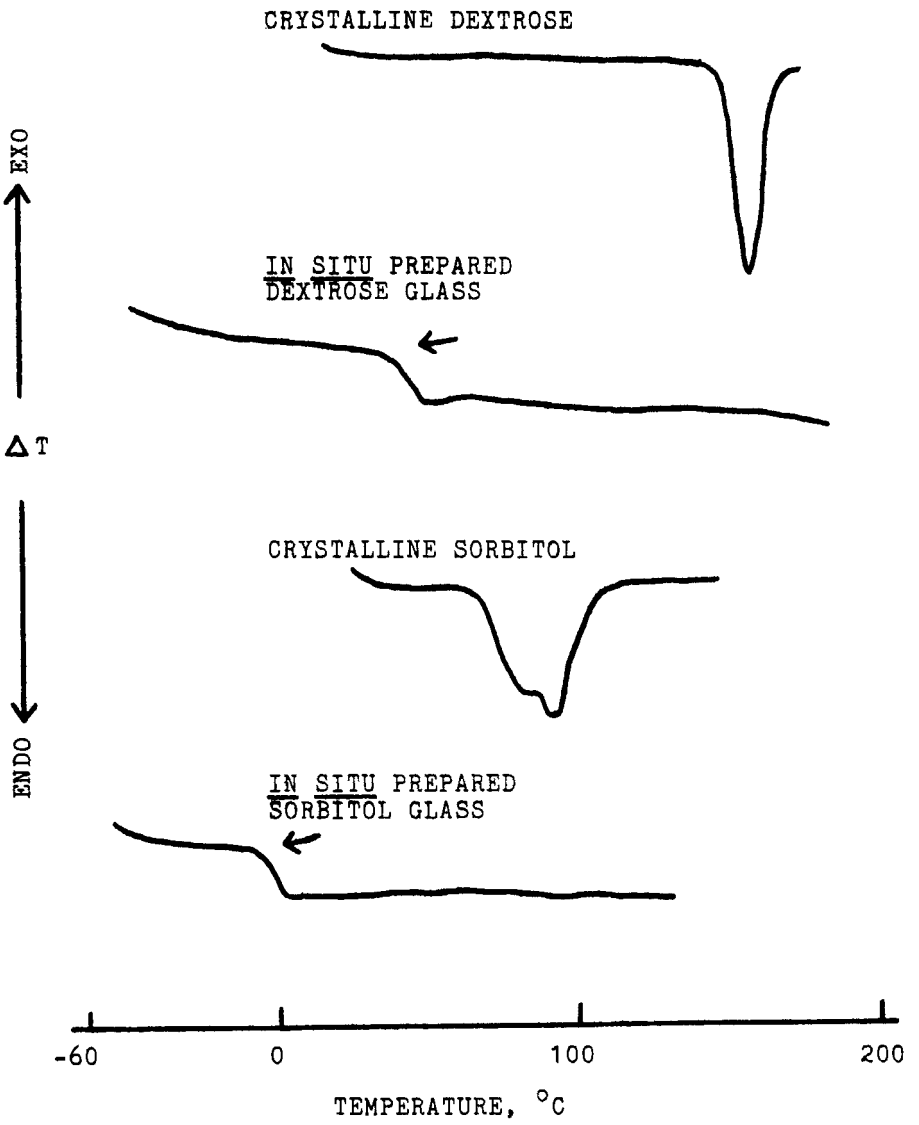


FIGURE 1

Thermograms of Dextrose and Sorbitol
The Glass Transition Temperatures are Indicated by Arrows.

systems in which neither material formed a glass, rather, it dealt with the first two possibilities.

Three test vehicles, citric acid, dextrose, and sorbitol, were used in this study. These materials exhibit varying chemical properties and each readily forms a glass. A thermogram of glassy citric acid has been reported previously (9), those of dextrose and sorbitol are shown in Figure 1.

The thermogram for glassy dextrose, which is similar to that reported by Miller (20), exhibits a glass transition at about 37°C followed by gradual softening. Glassy dextrose did not crystallize during normal handling, was stable to mechanical manipulation, but did have a tendency to absorb moisture if left unprotected under normal atmospheric conditions.

The thermogram of crystalline sorbitol shows two endothermic peaks, one at about 85°C and another at about 94°C. These temperatures correspond to the melting points reported for two polymorphic modifications of sorbitol (30). The thermogram of *in situ* prepared glassy sorbitol shows a glass transition at about -2°C. The material was thermally stable and did not crystallize as the temperature was raised.

The effect of crystalline additives on glassy dextrose is shown in Figure 2. These results are similar to those reported previously for benzoic acid

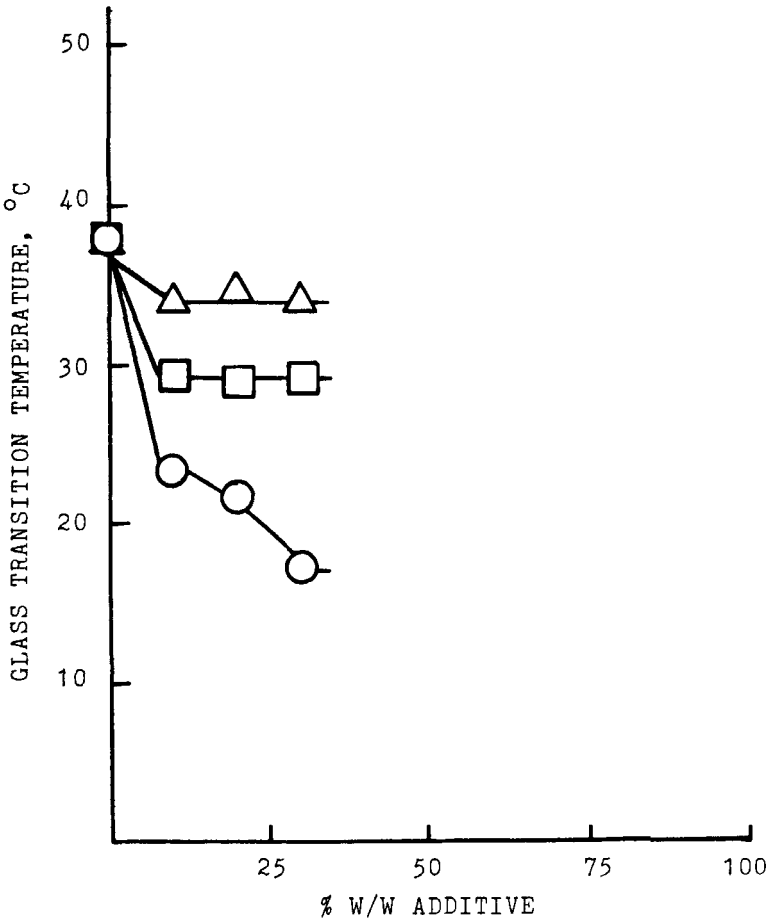


FIGURE 2

The Effect of Crystalline Additives on the Transition Temperature of Dextrose Glass Key: (△) Benzoic Acid; (□) Salicylamide; (○) Salicylic Acid

in glassy citric acid (9). In general, it was found that the addition of a crystalline drug into a glassy vehicle resulted in the reduction of the vehicle's glass transition temperature. The concentration of drug in vehicle above which the Tg did not further decrease can be considered the limit of incorporation

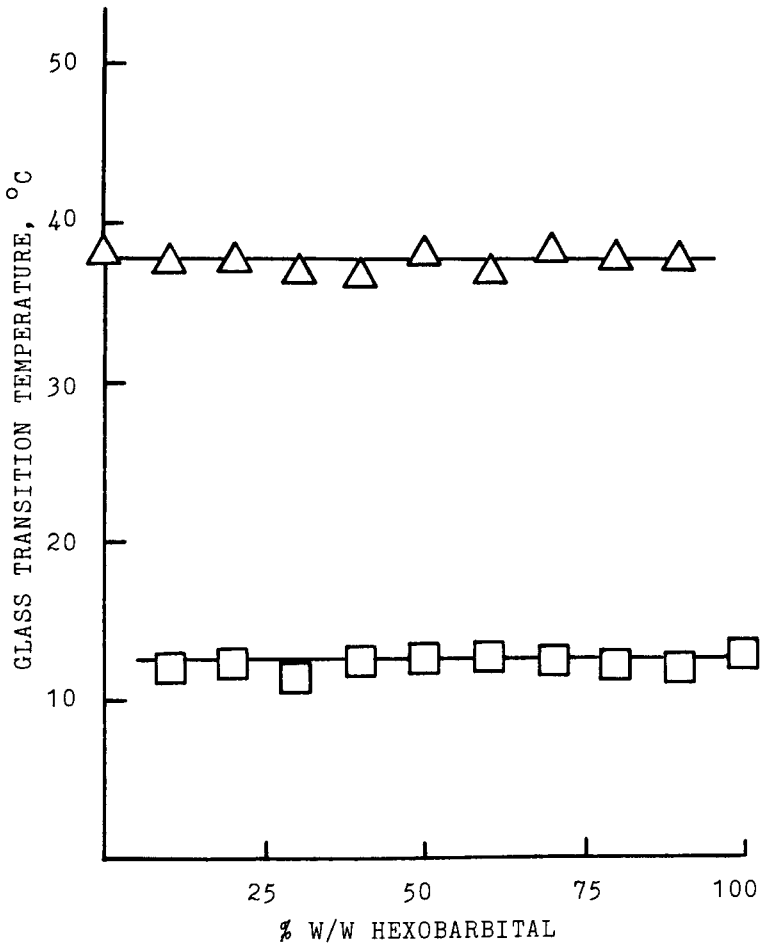


FIGURE 3

The Transition Temperatures for the Hexobarbital-Dextrose Glass System Key: (△) Dextrose; (□) Hexobarbital

of drug into the vehicle. The amount of drug that could be incorporated appeared to be related to its degree of association with the vehicle. The glass transition temperature reduction can be hypothesized to result from a disruption in the inter-molecular bonding in the glassy matrix due to the presence of

the crystalline drug. As the concentration of the drug increased, more and more breakdown of the glassy structure occurred, eventually resulting in the crystallization of the molten mixture upon cooling.

The glassy states of glass-forming compounds were immiscible, partially miscible, or totally miscible. Immiscible glasses showed little change in their transition temperatures with varying composition of their mixtures. An example of this behavior is the hexobarbital-dextrose system shown in Figure 3. The thermograms for this system (Figure 4) show two glass transition temperatures, one at about 13°C and one at about 37°C, the glass transitions of the pure compounds. Visual observation of the melts of this system indicated that they contained two distinct phases, with one floating on the other.

Mixtures of partially miscible glasses exhibited a single glass transition for those combinations of the materials which were below the limits of miscibility, and glass transitions attributable to each component in combinations which exceeded the limits of miscibility. This behavior was observed with a variety of systems which included dextrose-acetaminophen, sorbitol-acetaminophen, and sorbitol-phenobarbital. Visual observation of melts of these systems indicated for the combinations which showed a single glass transition tem-

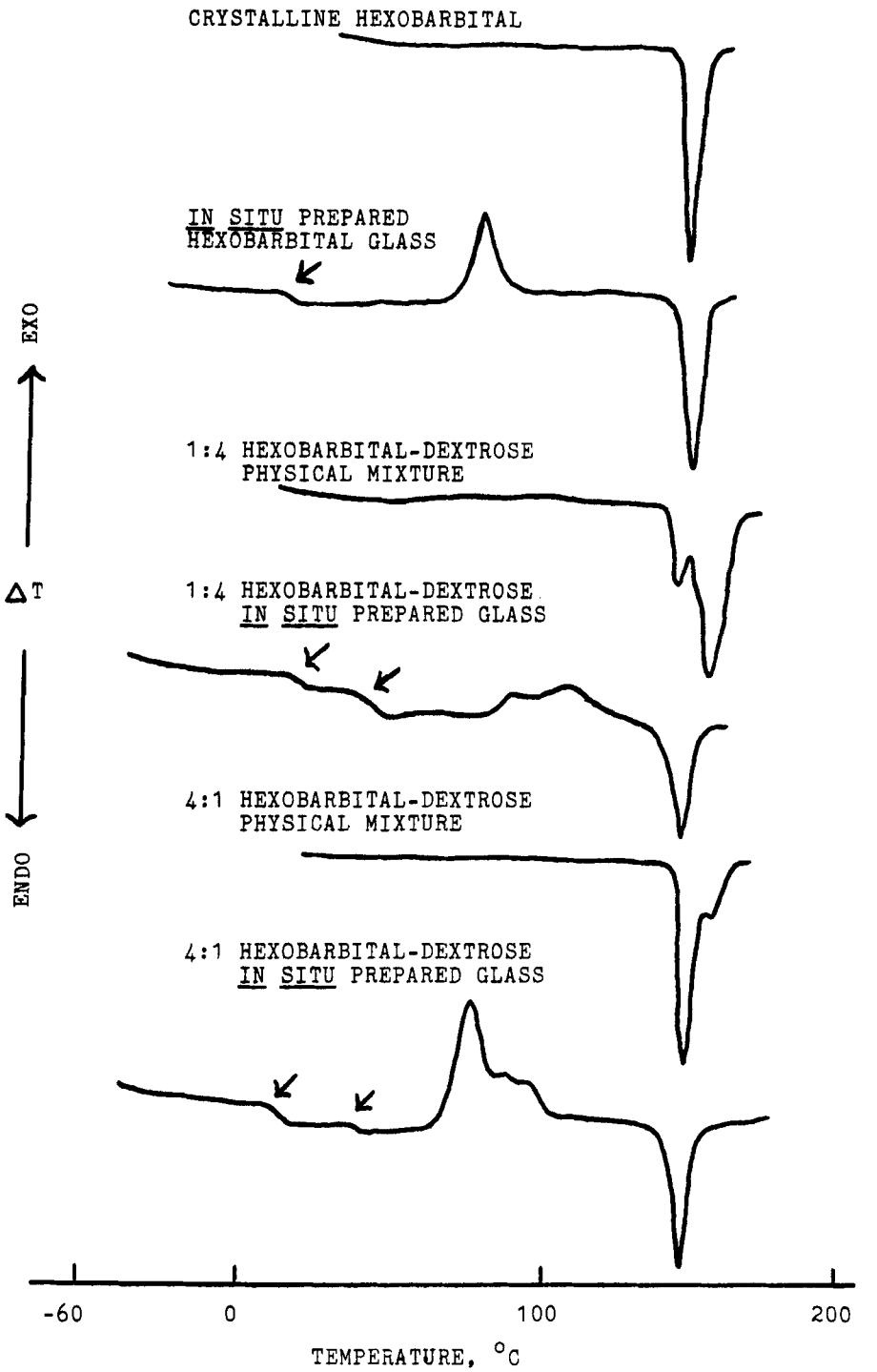


FIGURE 4

Thermograms of the Hexobarbital-Dextrose Dispersion System. The Glass Transition Temperatures are Indicated by Arrows.

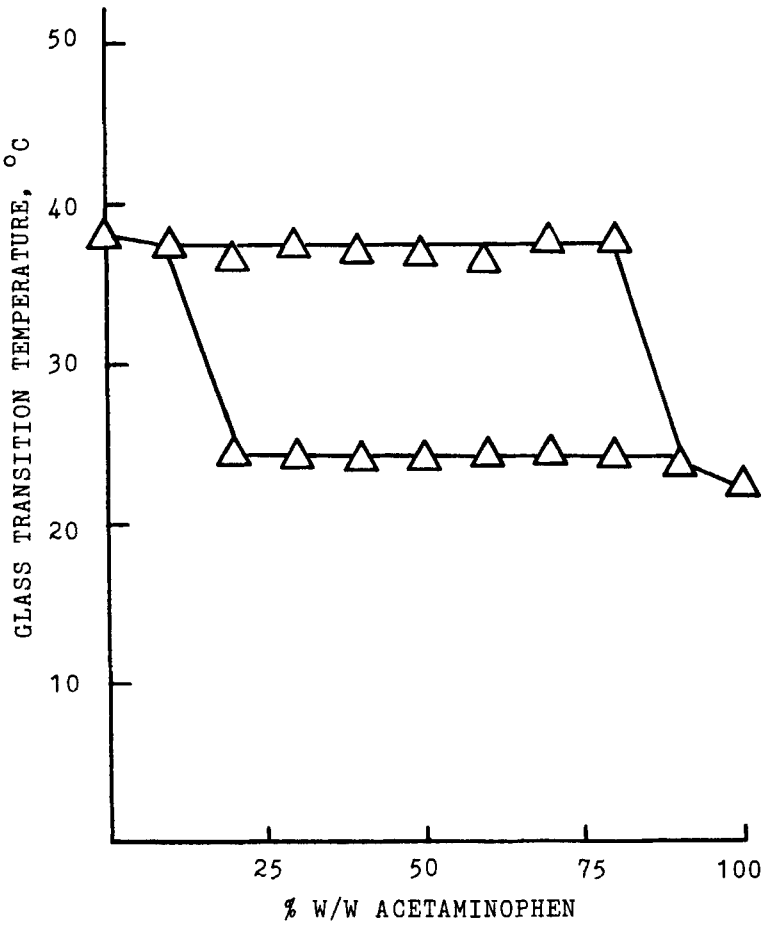


FIGURE 5

The Transition Temperatures for the Acetaminophen-Dextrose Glass System

perature, the melts were clear, transparent, and a single phase while those with two glass transitions appeared to be two phases with globules of one phase dispersed in the other. Figures 5 and 6 show the glass transition and thermogram data for the dextrose-acetaminophen system.

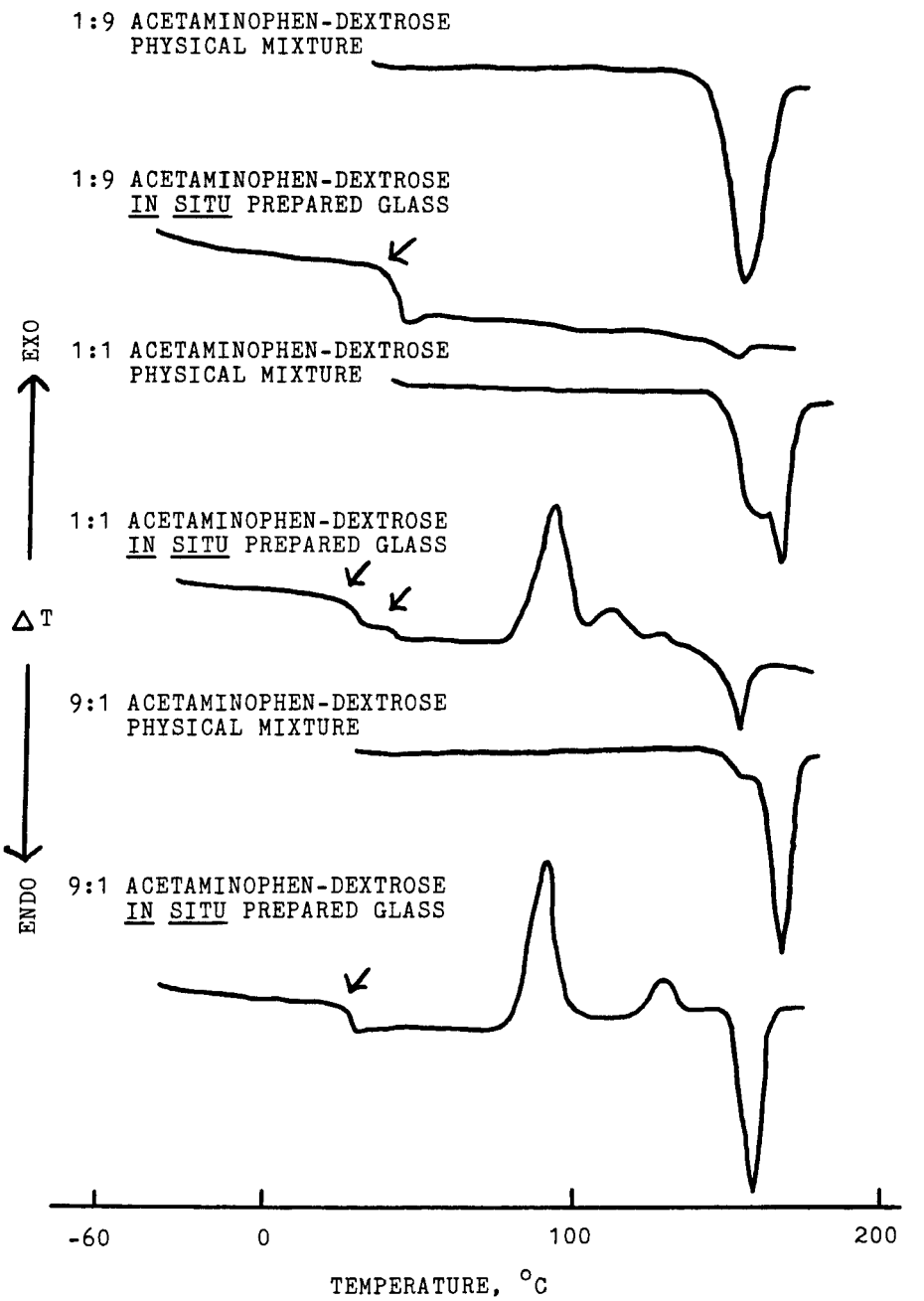


FIGURE 6

Thermograms of the Acetaminophen-Dextrose Dispersion System. The Glass Transition Temperatures are Indicated by Arrows.

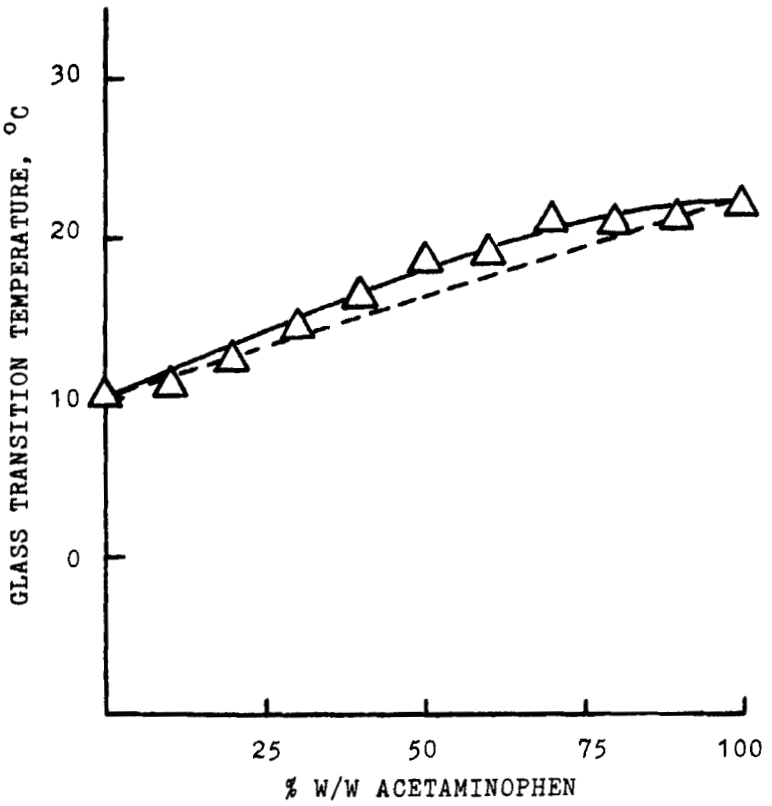


FIGURE 7

The Transition Temperatures for the Acetaminophen-Citric Acid Glass System. The Dashed Line Represents the Values of the Glass Transition Temperatures Predicted by Eq. 1.

Glassy systems which were totally miscible exhibited a single glass transition temperature for all combinations of the materials as illustrated with the citric acid-acetaminophen system (Figure 7). Similar results were obtained for the amobarbital-citric acid, pentobarbital-citric acid, and hexobarbital-citric acid mixtures. In fact, the transition temperature of a

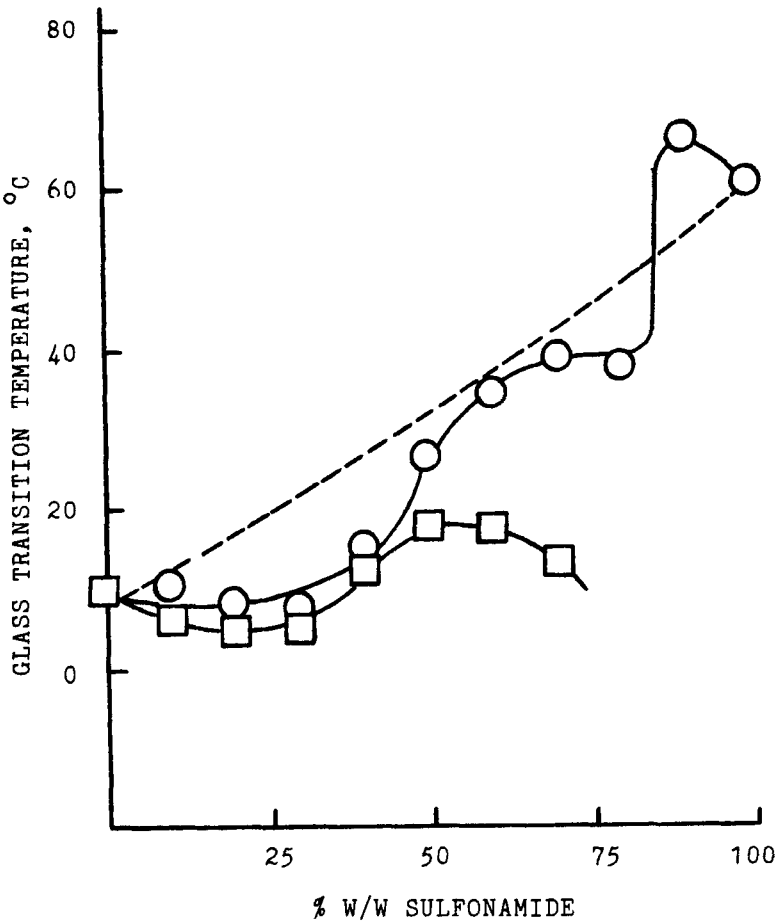


FIGURE 8

The Transition Temperatures for the Sulfonamide-Citric Acid Glass Systems Key: (□) Sulfanilamide; (○) Sulfathiazole. The Dashed Line Represents the Values of the Transition Temperatures for the Sulfathiazole-Citric Acid System Predicted by Eq. 1.

mixture of two randomly mixed compatible miscible glasses was between the transition temperatures of its individual glassy components. This is similar to two randomly mixed polymeric materials which adhere to the widely used relationship (31):

$$\frac{1}{Tg} = \frac{Wa}{(Tg)a} + \frac{Wb}{(Tg)b} \qquad \text{(Eq. 1)}$$

where (Tg)a and (Tg)b are the glass transition temperatures of the two components of the mixture in degrees Kelvin, and Wa and Wb are their respective weight fractions. Some deviation from the predicted value does occur but this may be due to differences in bonding or association between like and unlike molecules.

Glassy mixtures which showed wild fluctuations in transition temperatures either less than or greater than the transition temperatures of its glassy components, as seen with the sulfonamide-citric acid (Figure 8) or sulfonamide-dextrose (Figure 9) mixtures, suggest a reaction and/or incompatibility between the materials. It was observed that melts of the sulfonamides in citric acid or dextrose developed a burnt orange color as the proportion of sulfonamide increased in the mixtures. Previous studies with sulfamethoxazole (7) suggest possible interaction between sulfonamides and compounds containing carbonyl groups.

Most of the glasses examined in this study were mechanically and/or thermally unstable. By mixing two compatible miscible glasses, it was possible to obtain greater physical stability than could be realized from the individual glassy components. This was demonstrated in particular by the acetaminophen-citric acid system.

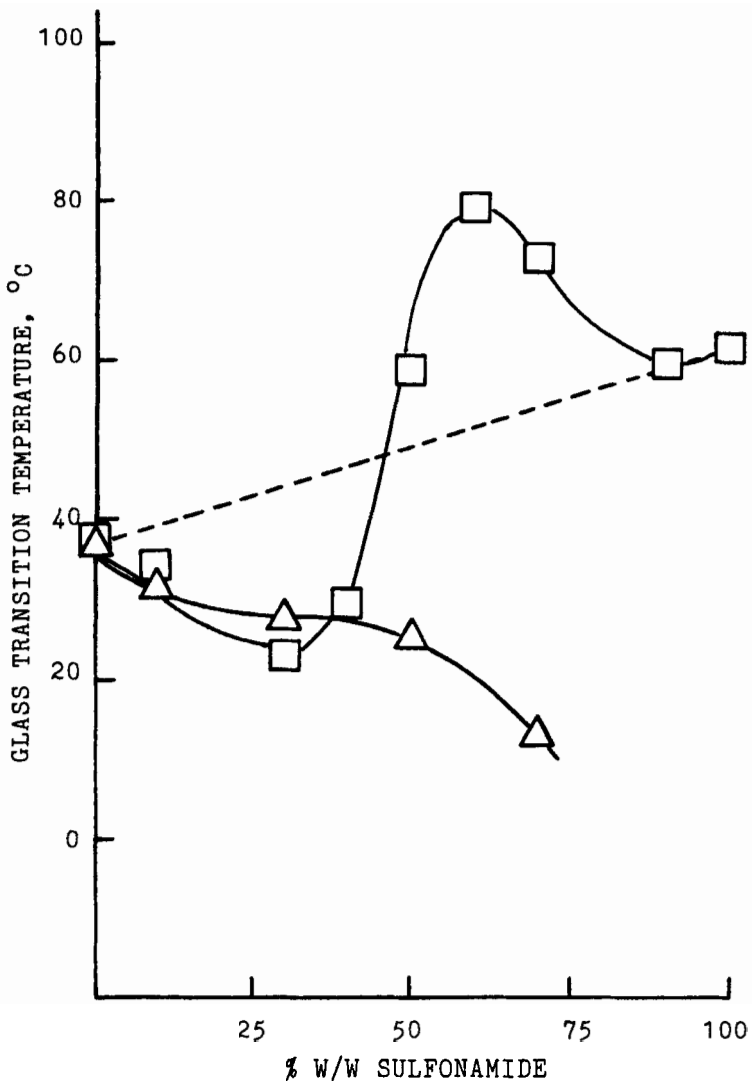


FIGURE 9

The Transition Temperatures for the Sulfonamide-Dextrose Glass Systems Key: (△) Sulfanilamide; (□) Sulfathiazole. The Dashed Line Represents the Values of the Glass Transition Temperatures for the Sulfathiazole-Dextrose System Predicted by Eq. 1.

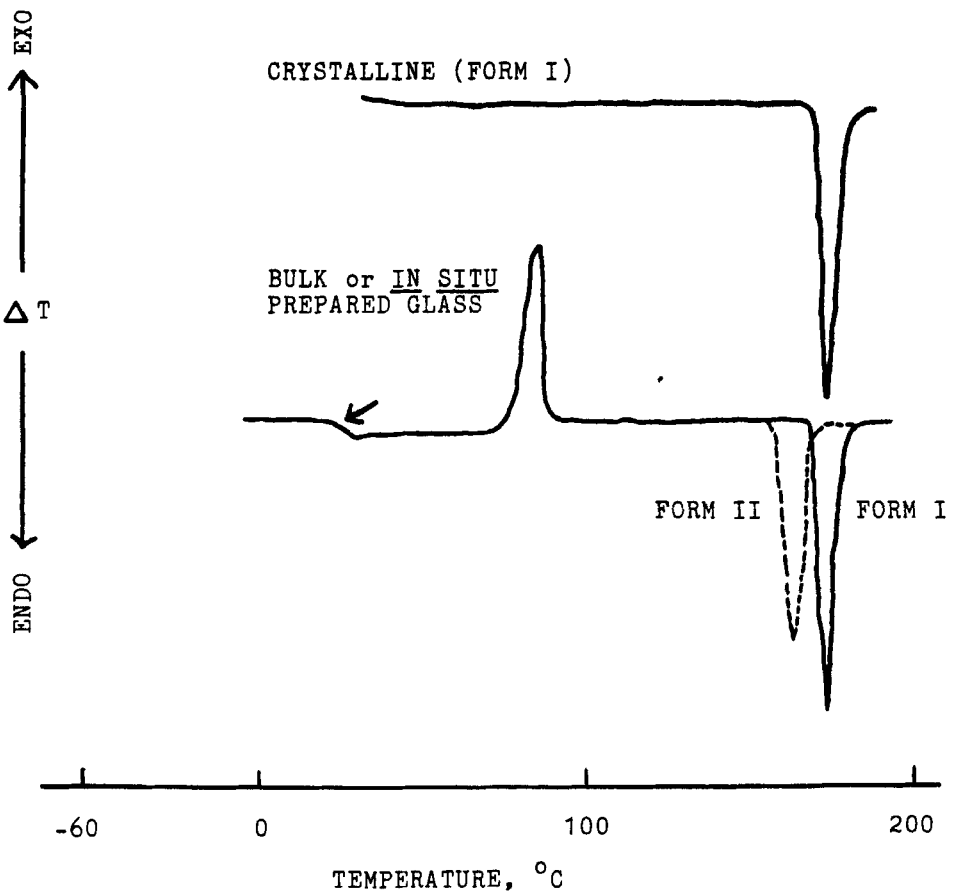


FIGURE 10

Thermograms for Acetaminophen
The Glass Transition Temperature is Indicated by an Arrow.

Acetaminophen glass is both mechanically and thermally unstable. It crystallized and melted when the temperature was raised above its glass transition temperature, as shown by the large crystallization exotherm in its thermogram (Figure 10). The endothermic peak temperatures correspond to the melting points

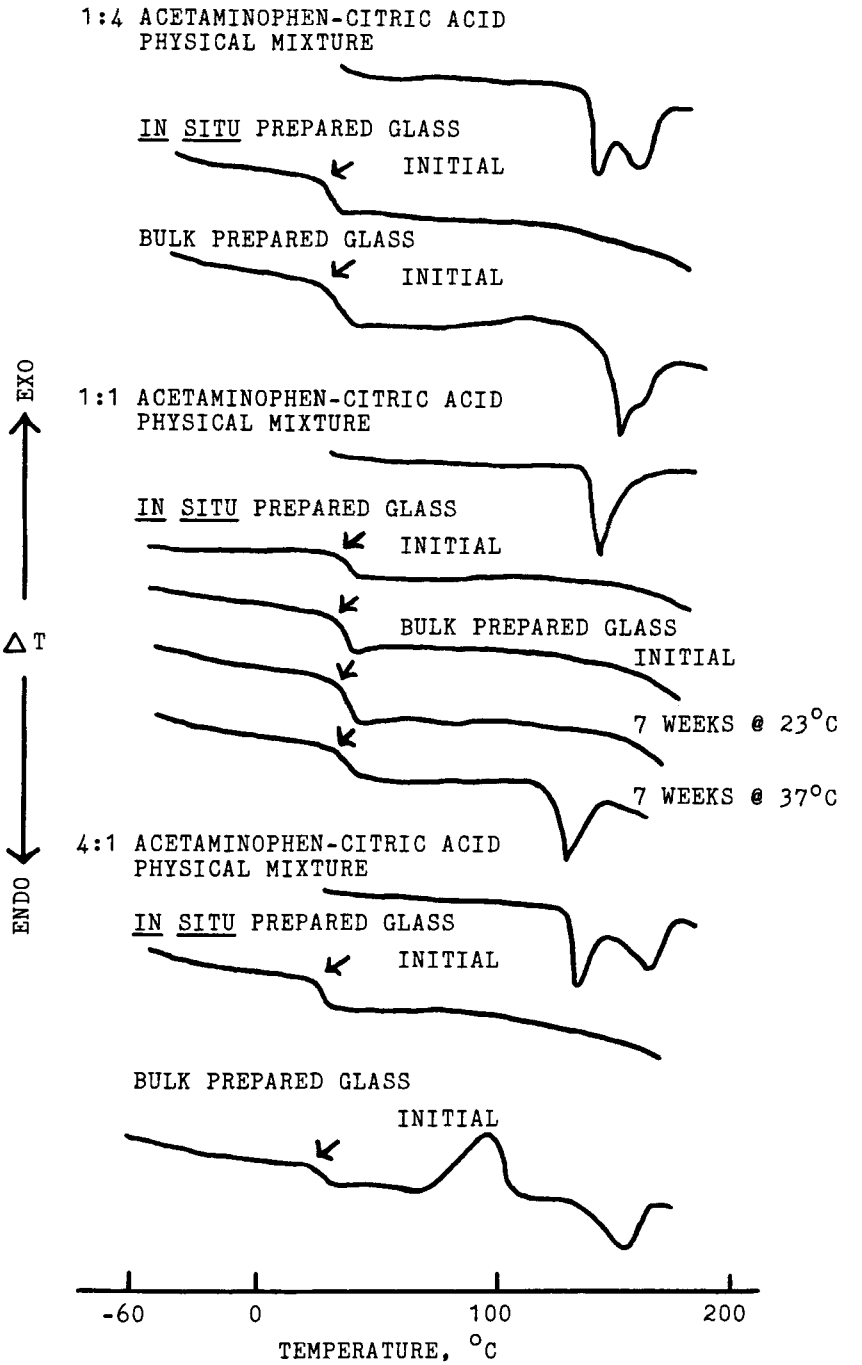


FIGURE 11

Thermograms for the Acetaminophen-Citric Acid Glass System. The Glass Transition Temperatures are Indicated by Arrows.

reported for its two polymorphic modifications (32). Attempts to prepare bulk quantities of acetaminophen glass were not very successful. Glassy acetaminophen began to crystallize almost immediately after preparation and handling. Devitrification was generally complete within 48 hours.

On the other hand, and as previously reported (9), although citric acid is also mechanically unstable, it takes considerably longer for complete devitrification. Glassy samples held at room temperature were still partially amorphous after 60 days.

Thermograms of the acetaminophen-citric acid glass system are shown in Figure 11. Thermograms of the 1:4 and 4:1 acetaminophen-citric acid bulk prepared solidified melts showed indications that they were mechanically unstable. The thermogram for the 1:1 acetaminophen-citric acid bulk prepared melt is essentially identical to that of the in situ prepared mixture. Handling did not induce crystallization. Aged samples of the 1:1 acetaminophen-citric acid bulk prepared glass mixture stored at 23°C showed no changes in their thermograms after seven weeks of storage. Samples stored at 37°C for seven weeks exhibited some devitrification. The Tg of this mixture is about 18°C

## SUMMARY AND CONCLUSIONS

Since glasses are supercooled liquids, the results

observed among the glass forming materials investigated in this study can be explained by miscibility among liquids. The addition of crystalline additive to a glassy vehicle can be viewed as a solid solute in a liquid solvent.

Most of the glasses examined were thermally and/or mechanically unstable. As demonstrated by the acetaminophen-citric acid system, by combining two compatible miscible glasses in the proper ratio, it was possible to obtain greater physical stability than could be realized by either of its glassy components.

The glass dispersion technique is presently in the developmental stages, and a number of technical problems must be overcome before its full potential can be achieved. The sample sizes used in this study were relatively small and, at times, were still difficult to rapidly cool and handle. A method must be devised to melt and then cool large quantities of material with sufficient rapidity so as to prevent crystallization. In addition, the bulk volume of these systems must be reduced to aid in their formulation into solid dosage forms. The ideal extension of this technique is the stabilization of the glassy state of a glass-forming drug by mixing it with minimal amounts of an inert compatible material.

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## FOOTNOTES

1. NF, Amend Drug and Chemical Co., Inc., New York, N.Y.
2. Ruger Chemical Co., Inc., Irvington, N.J.
3. USP, Fisher Scientific Co., Springfield, N.J.
4. Certified ACS, Fisher Scientific Co., Springfield, N.J.
5. Reagent Grade, Fisher Scientific Co., Springfield, N.J.
6. Sigma Chemical Co., Inc., St. Louis, Mo.
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10. J.T. Baker Chemical Co., Phillipsburg, N.J.
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14. DuPont 900 Thermal Analyzer with a No. 900600 Differential Scanning Calorimeter Cell, E.I. DuPont DeNemours and Co., Wilmington, Del.
15. E.I. DuPont DeNemours and Co., Wilmington, Del.
16. E.I. DuPont DeNemours and Co., Wilmington, Del.
17. E.I. DuPont DeNemours and Co., Wilmington, Del.
18. E.I. DuPont DeNemours and Co., Wilmington, Del.

19. Catalog No. 900786-901, E.I. DuPont DeNemours and Co., Wilmington, Del.

20. Catalog No. 900779-901, E.I. DuPont DeNemours and Co., Wilmington, Del.

21. Sunbeam Corp., Chicago, Ill.

22. Catalog No. 12-1570-01, Ace Scientific Supply Co., Inc., East Brunswick, N.J.

23. Catalog No. 08-595D, Fisher Scientific Co., Springfield, N.J.

24. Certified ACS, Fisher Scientific Co., Springfield, N.J.

25. Type TG-2, Erweka-G.m.B.H., Frankfurt, West Germany

26. 30cc, square, widemouth, with black phenolic caps and P-V liner, J. Rabinowitz and Sons, Brooklyn, N.Y.

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