graphically for the presence of any extractable ethyl acetate UV-absorbing (313 nm) material that might interfere with tinidazole measurement.

RESULTS AND DISCUSSION

A successful chromatographic assay for drug levels in the large number of plasma samples generated from a clinical study would provide highly reproducible drug recovery, specificity, sensitivity, precise measurement, and rapid throughput of samples.

The average recovery of drug from plasma samples to which tinidazole had been added was 86.9 ± 2.8% *SD* (Table I). Linear regression analysis of percent recovery *versus* plasma concentration revealed no statistically significant slope (β) ($p = 0.7431$). These data, therefore, suggest that there is no concentration dependence on extraction efficiencies over the range of expected plasma drug levels (10–12).

Tinidazole was monitored at 313 nm since its λ_{max} was observed in methanol at 310 nm ($\epsilon = 9070$). Ethyl acetate extracts from drug-free plasma were free of interfering UV- (313 nm) absorbing peaks (Fig. 1). Preextraction with petroleum ether eliminated nonpolar material that would otherwise be highly retained on this reversed-phase system. Little or no loss of tinidazole was encountered in this step.

Baseline resolution among tinidazole, II, and III was achieved under the chromatographic conditions described (Fig. 2). The observed retention times (t_r) for III, II, and I were 2.73, 6.12, and 8.96 min, respectively. Representative chromatograms of plasma extracts containing 0.20 and 20.0 μg/ml of tinidazole are shown in Fig. 3.

Linear regression analysis of the curve described by plotting microvolt-seconds (area) *versus* micrograms injected indicated a linear fit of the data ($r^2 = 0.9994$) from 0.025 to 0.25 μg. The slope was 474.75 μv-sec/ng; the intercept, which was not significantly different from zero ($p < 0.05$), was 1512 μv-sec. Over 2 months, the slope of this line demonstrated little change, with a coefficient of variation equal to 3.83% ($n = 16$).

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ACKNOWLEDGMENTS

The authors thank Dr. B. A. Wood of Pfizer Ltd., Sandwich, Kent, England, for providing samples of tinidazole metabolites.

Thermal Characterization of Citric Acid Solid Dispersions with Benzoic Acid and Phenobarbital

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Received April 24, 1978, from the *College of Pharmacy, Rutgers—The State University, Busch Campus, Piscataway, NJ 08854.* Accepted for publication October 25, 1978.

Abstract □ The glass transition temperatures of citric acid glass were determined by differential scanning calorimetry to be 10.2 and 13.5° for *in situ* and bulk-prepared samples, respectively. Mechanical stress on citric acid glass induced foci for crystallization. Benzoic acid addition to citric acid glass decreased its glass transition temperature while phenobarbital addition increased its glass transition temperature, the latter forming a glass solution.

Keyphrases □ Glass transition temperature—citric acid glass, benzoic acid, mechanical stress, phenobarbital □ Citric acid—glass formation, glass transition temperature, benzoic acid, phenobarbital □ Glass formation—citric acid, benzoic acid, phenobarbital □ Phenobarbital—glass formation with citric acid

A glass is generally defined as a noncrystalline solid formed by continuous hardening or solidification of a liquid (1, 2). The use of organic compounds capable of glass formation to reduce the particle size of a drug and to increase its dissolution and absorption rates was first suggested by Chiou and Riegelman (3). They proposed the formation of a glass dispersion of a poorly water-soluble drug and a physiologically inert carrier such as citric acid. The concepts involved in glass solution and glass suspension formation were discussed previously (4).

Glass dispersions are metastable and, as a result, exhibit rapid dissolution. In a study with griseofulvin (3), the citric acid–griseofulvin glass solution had the fastest dissolution rate of the solid dispersion systems examined. However, griseofulvin decomposition occurred in the presence of citric acid during manufacturing. Citric acid was also an unacceptable sulfabenzamide carrier (5). As with griseofulvin, thermal drug degradation occurred during sample preparation.

Summers and Enever (6–8) studied citric acid–primidone glass dispersions and found the glass solutions formed to be unstable and rapidly devitrified. The devitrified dispersion systems, however, still exhibited more rapid dissolution than the pure drug or drug and carrier mixtures. The citric acid glass transition temperature increased with increasing primidone concentration (8). The

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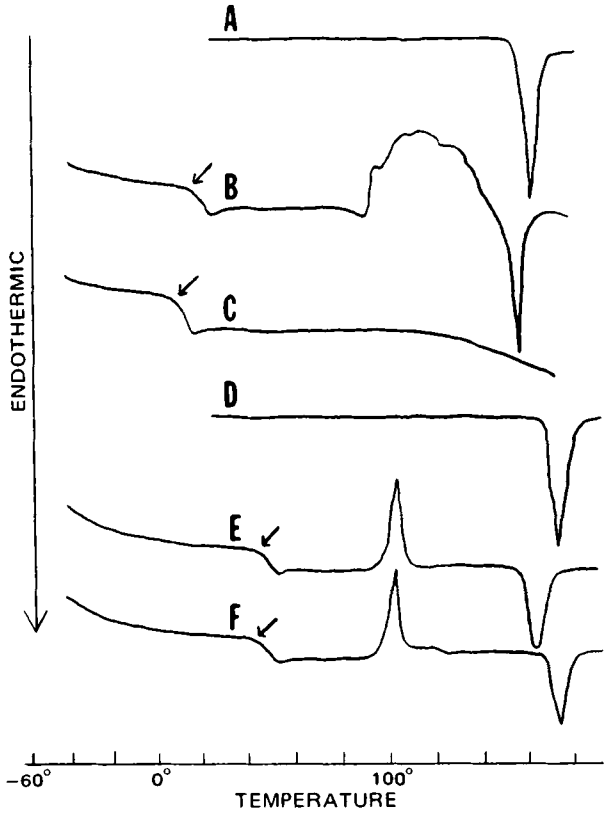

Figure 1—*Thermograms of anhydrous citric acid (A), bulk-prepared citric acid solidified melt (B),* in situ *prepared citric acid glass (C), phenobarbital (D),* in situ *prepared phenobarbital glass crystallizing as polymorphic Form IV (E), and* in situ *prepared phenobarbital glass crystallizing as polymorphic Form I (F). The glass transition temperatures are indicated by arrows.*

increased primidone dissolution rate was a result of its reduced particle size and increased wettability in the systems.

Most glass dispersion studies concentrate on the drug. Little information is available on carrier stability or the effect of additives on stability. This article reports some observations on citric acid glass stability; the effect of two additives, benzoic acid and phenobarbital, on its glass transition temperature; and the nature of the dispersion systems these materials form. Benzoic acid, a crystalline material, has not been reported capable of glass formation. Phenobarbital has been suggested to be capable of glass formation by rapid melt cooling (9) and has been reported to form a glass solution with citric acid (3).

EXPERIMENTAL

Materials—Citric acid[1] (mp 152–156°), benzoic acid[2] (mp 121–124°), and phenobarbital[3] (mp 174–178°) were used as received.

Thermal Analysis—A differential scanning calorimeter[4] was used to determine the glass transition temperatures and stabilities. Observed temperature values were corrected for chromel alumel thermocouples from −60 to 200° using indium metal as the standard. All determinations were made at least in duplicate.

A 10–15-mg sample size was necessary to obtain reproducible and distinct transition temperatures. Samples were scanned at 10°/min in a static air atmosphere using an empty aluminum pan as the reference.

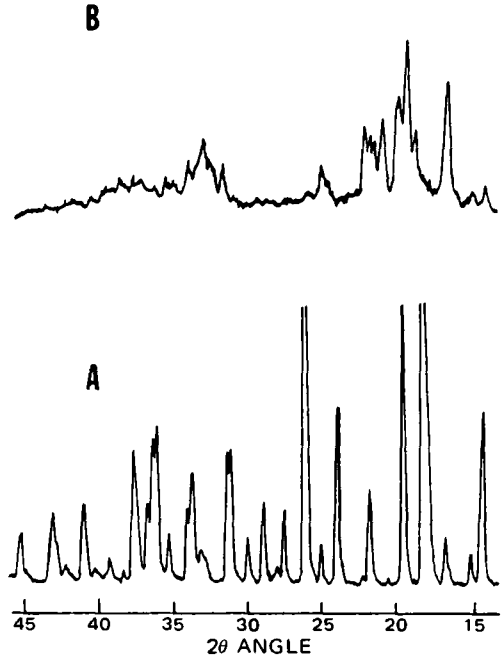

Figure 2—*X-ray diffraction pattern of anhydrous citric acid (A) and bulk-prepared citric acid solidified melt (B).*

The sensitivities were 1.0°/in. for pure materials and physical mixtures and 0.2°/in. for solidified melts and glass systems. A 20°/in. temperature scale was used.

Two procedures were used for sample preparation, an *in situ* method and a bulk procedure. In the *in situ* procedure, citric acid or mixtures of citric acid and benzoic acid or phenobarbital in the desired ratio were weighed accurately directly into an aluminum sample pan. An aluminum cover was placed on the sample, and the pan was transferred to the sample holder of the differential scanning calorimeter. After the sample was heated to melting, the melt was rapidly cooled to −60° by purging the sample holder of the instrument with liquid nitrogen. The solidified melt was reheated, and the thermogram was recorded.

Bulk glass system preparation involved melting 50 g of citric acid or mixtures of citric acid and benzoic acid or phenobarbital in the desired ratio in an electric frying pan[5] heated to 170°. Samples were stirred continually until melting was complete. The melt was rapidly solidified by transferring it to an aluminum foil boat located on a dry ice block hollowed out to fit the boat dimensions. After solidification, the melt was removed from the dry ice and placed in a desiccator over silica gel at 23° for 24 hr. The solidified melt was pulverized in a rotary granulator[6].

Samples of the solidified melts, prepared by both the *in situ* method (removed from the sample holder after cooling to −60°) and the bulk procedure, were placed in desiccators at 4, 23, and 37°. Thermograms were run periodically to examine the effects of aging on physical stability.

The melting temperatures of the physical mixtures were determined by differential scanning calorimetry and a conventional capillary tube melting-point apparatus[7]. Both the onset of melting temperature and the complete fusion temperature are reported. When using the differential scanning calorimetry, melting onset was defined as the temperature at which there was an initial endothermic deviation in the thermogram baseline. Its value was the curve extrapolation crossing point on each side of the baseline deviation. The complete fusion temperature was the endothermic peak temperature. If a sharp peak was not obtained, the sides of the peak were extrapolated and the crossing point was used as the value of the endothermic peak. With the capillary tube method, the melting onset and the complete fusion temperatures were visually estimated with a magnifying glass. The heating rate was ~10°/min.

The area under the exothermic peak in the bulk-prepared citric acid melts was determined by a cut and weigh method. Areas were calculated according to the standard area weight. Results are reported as area under the peak in square centimeters per milligram of sample weight.

[1] Anhydrous, J. T. Baker Chemical Co., Phillipsburg, N.J.
[2] Reagent grade, Fisher Scientific Co., Fair Lawn, N.J.
[3] USP, Mallinckrodt Chemical Works, St. Louis, Mo.
[4] DuPont 900 thermal analyzer with a No. 900600 differential scanning calorimeter cell, E. I. DuPont DeNemours and Co., Wilmington, Del.
[5] Sunbeam Corp., Chicago, Ill.
[6] Type TG-2, Erweka-G.m.b.H., Frankfurt, West Germany.
[7] Model JM-110, Scientific Glass Inc., Bloomfield, N.J.

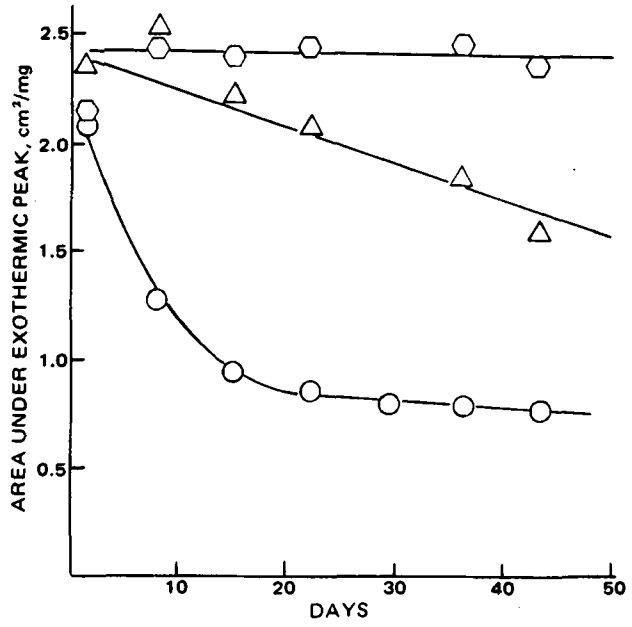

Figure 3—*Storage temperature effect on the area under the exothermic peak of bulk-prepared citric acid solidified melt. Key:* ○, *4°;* △, *23°; and* ○, *37°.*

X-Ray Diffraction—An X-ray diffractiometer[8] was used to determine the bulk-prepared solidified citric acid melt. Powdered mixed particle-size samples were mounted on a screen sample holder, and the X-ray diffraction pattern was determined using Cu K_α radiation. A powdered citric acid sample was run for comparison.

NMR Studies—Citric acid stability during sample preparation was examined by NMR[9]. The fused sample citric acid spectra, prepared by both the *in situ* and bulk methods, were compared with those of unfused citric acid and aconitic acid[10], a possible dehydration decomposition product of citric acid. The solvent was deuterium oxide, and tetramethylsilane was the internal standard.

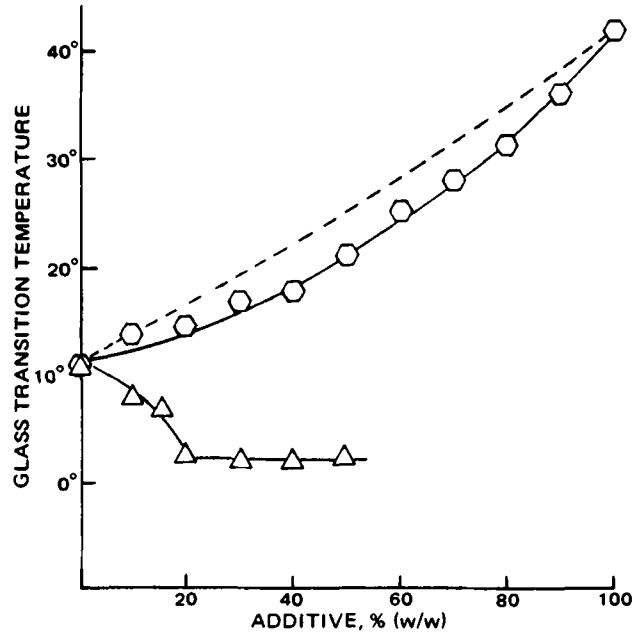

Figure 4—*Effect of benzoic acid (*△*) and phenobarbital (*○*) on the citric acid glass transition temperature. The dashed line represents the values of the glass transition temperatures of the phenobarbital–citric acid glass system predicted by Eq. 1.*

[8] Model GE XRD-6, General Electric Co.
[9] Varian T-60 NMR spectrometer, Varian Instrument Division, Palo Alto, Calif.
[10] Aldrich Chemical Co., Milwaukee, Wis.

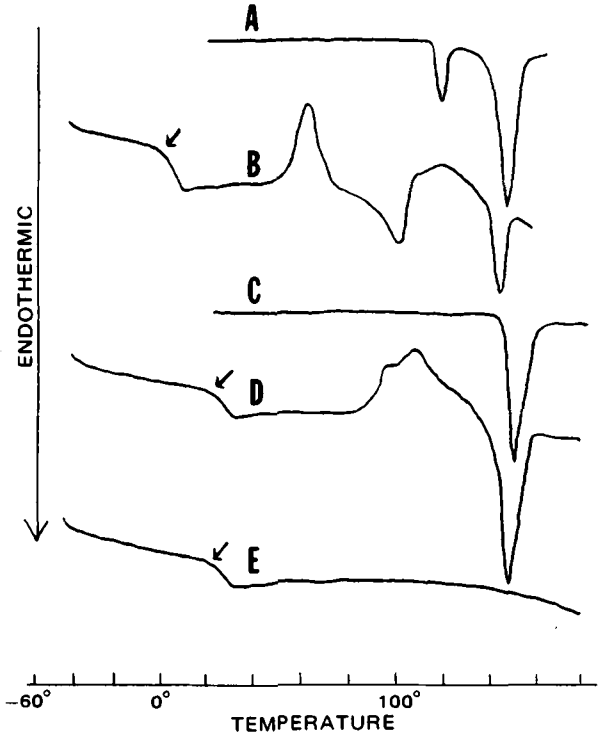

Figure 5—*Thermograms of 1:4 benzoic acid–citric acid physical mixture (A), 1:4 benzoic acid–citric acid* in situ *prepared glass (B), 1:1 phenobarbital–citric acid physical mixture (C), 1:1 phenobarbital–citric acid bulk-prepared solidified melt (D), and 1:1 phenobarbital–citric acid* in situ *prepared glass (E). Glass transition temperatures are indicated by arrows.*

RESULTS AND DISCUSSION

Glass is a fourth state of matter, distinct from both the crystalline and liquid states, yet exhibiting characteristics of both. Like a crystal, a glass exhibits ridigity; like a liquid, it has random molecular arrangement (1, 10, 11).

The crystalline and liquid states are delineated from each other by a definite temperature: the melting point of the crystalline material. The transition between a glass and a liquid is more ambiguous (12). In differential scanning calorimetry, it is indicated by a marked shift in the thermogram baseline due to an increase in the material's specific heat. The glass transition temperature (T_g) is the upper boundary of this transitional temperature range (10), and it is this temperature that is reported as the T_g of the glass system studied. Experimentally, it was determined by extrapolating the curve on each side of the onset of the baseline shift; the crossing point of the extrapolated lines was used as the T_g value.

Crystalline citric acid is highly hydrogen bonded (13). Citric acid glass formation has been attributed to this hydrogen bonding capacity, which may prevent its crystallization (14). Citric acid glass formation may be due also to its partial decomposition by dehydration into aconitic acid during melting (4).

Citric acid stability during sample preparation was examined by NMR. No changes were observed in the fused citric acid spectra when compared to the spectrum of unfused citric acid. A molten citric acid sample held isothermally at 175° for 5 min and then cooled rapidly also showed no spectral changes. The thermogram of this material was identical to that of citric acid melt prepared in the normal manner.

Thermal citric acid studies indicate possible anhydride formation on continuous heating at ~185° (15). Decomposition does not occur until about 200° (15, 16), where citric acid begins to decompose to a mixture of itaconic and citraconic acid anhydrides.

The thermograms of bulk-prepared citric acid melt and *in situ* prepared citric acid glass are shown in Fig. 1. The bulk and *in situ* glass transitions were 13.5 and 10.2°, respectively. These results are in conflict with a previously reported T_g of −23° for bulk-prepared citric acid glass (8). In preliminary studies with bulk-prepared citric acid melts, a small baseline shift was observed at −23°, in addition to the transition at 13.5°, when the heating rate was 2°/min. Since this shift was not observed at

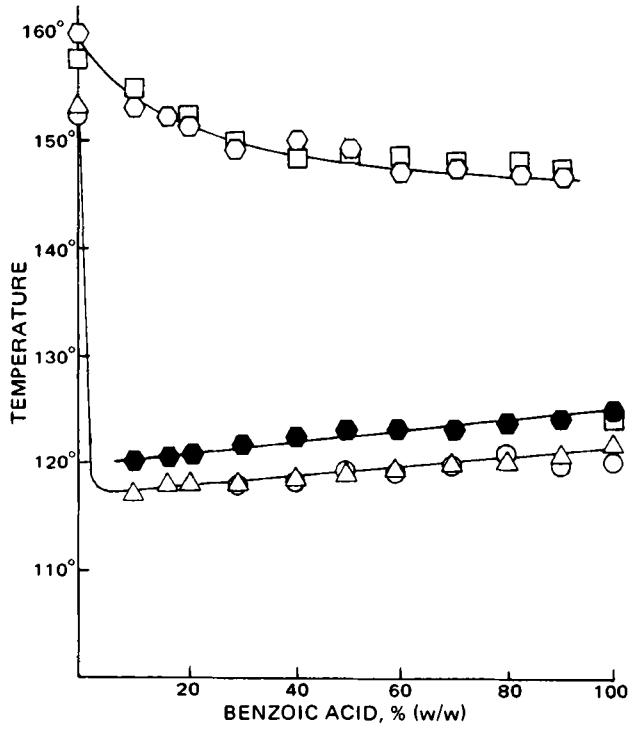

Figure 6—*Melting temperatures of the benzoic acid–citric acid binary system determined from physical mixtures. Key (differential scanning calorimetry): △, initial endothermic temperature deviation in the thermogram baseline; ○, citric acid endothermic peak temperature; and ●, endothermic benzoic acid peak temperature. Key (capillary tube method): ○, melting onset temperature; and □, complete physical mixture fusion temperature.*

heating rates of 5, 10, and 20°/min, it was not considered to be the true citric acid glass T_g but rather an artifact or a secondary transition in the sample as a result of molecular relaxation within the solidified melt (17).

The thermogram of the bulk-prepared melt exhibited a broad exothermic transition, onset at ~80°, followed by an endotherm. The exotherm was present in all samples but varied in size and shape. The *in situ* samples did not exhibit an exotherm. No changes were observed in their thermograms after 4 weeks of storage under the test conditions. When the *in situ* sample surface was scratched with a metal probe and the scan was recorded, an exotherm similar to the one observed in the bulk samples was noted. X-ray diffraction data (Fig. 2) indicated that the bulk-prepared citric acid melt consisted of an amorphous and crystalline citric acid mixture. Mechanical manipulation of the citric acid melt during processing induced crystallization foci, and the exotherm in the bulk-prepared citric acid melt thermograms was due to crystallization. The endotherm was crystallized solid melting.

The bulk-prepared citric acid melt crystallization rate can be studied by monitoring the rate of change in area under the exothermic peak. The smaller the area, the more crystalline is the material. Although the areas under the peak differed among batches of bulk citric acid melt because of stress variability, similar trends were observed (Fig. 3). Little area change was observed in melt samples stored at 4°. At 23°, the area gradually decreased with time. At 37°, there was a rapid initial decrease followed by a slower rate of change. The abrupt change in slope corresponded to the disappearance of the glass transition. An initial rapid crystallization was followed by a slower secondary crystallization. Possibly, crystallites formed in the primary process were regrouped and a more perfect crystalline state was formed.

The benzoic acid effect on the citric acid glass T_g is shown in Fig. 4. Benzoic acid up to 20% (w/w) decreased the T_g. Above this concentration, the limit of benzoic acid incorporation into citric acid glass was reached, and no further T_g reduction was observed. Excess benzoic acid crystallized upon cooling of the melt, forming a macrocrystal dispersion in the citric acid–benzoic acid glass matrix and disrupting the glass system. Figure 5 shows thermograms of a benzoic acid–citric acid (1:4) mixture and its rapidly cooled melt. The glass system was thermally unstable; the components crystallized and then melted as the temperature was increased.

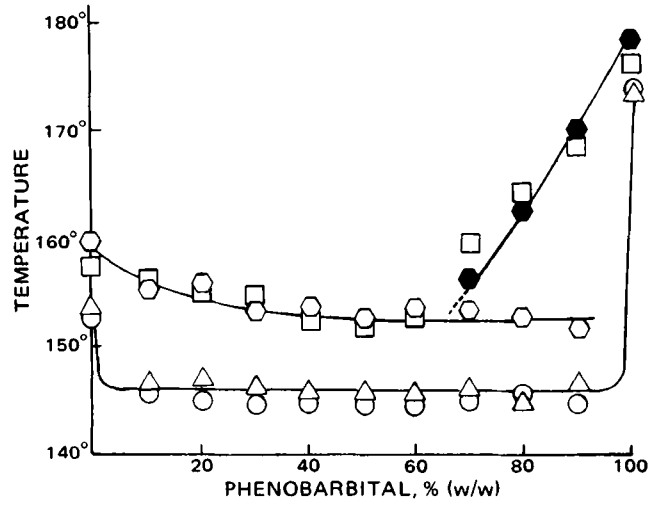

Figure 7—*Phenobarbital–citric acid binary system melting temperatures determined from physical mixtures. Key (differential scanning calorimetry): △, initial endothermic temperature deviation in the thermogram baseline; ○, citric acid endothermic peak temperature; and ●, phenobarbital endothermic peak temperature. Key (capillary tube method): ○, melting onset temperature; and □, complete physical mixture fusion temperature.*

The use of the melting characteristics of pharmaceutical mixtures to detect possible interactions between materials has been demonstrated (18, 19). Figure 6 shows the melting data for the benzoic acid–citric acid system. The results obtained by the capillary tube method were in good agreement with the melting onset and the complete fusion temperatures determined with the differential scanning calorimeter. Little interaction between benzoic acid and citric acid was indicated since the physical mixture melting temperatures showed little change when compared to the melting temperatures of the pure materials. The slight depression of the citric acid melting temperature in the mixtures was probably due to the presence of molten benzoic acid.

Phenobarbital also formed a glass on rapid cooling of its melt with a T_g of 41.9°. The thermograms (Fig. 1) showed an exotherm, onset at 90°, on continued heating above the T_g followed by an endotherm. The exotherm was attributed to crystallization, and the endotherm was attributed to crystallized phenobarbital melting. The phenobarbital crystallized into either of two polymorphic forms. A previous study of phenobarbital polymorphism showed similar results (9).

In polymeric systems, the mixture T_g of two miscible glasses can be estimated by (20):

$$\frac{1}{T_g} = \frac{W_a}{T_{ga}} + \frac{W_b}{T_{gb}} \qquad \text{(Eq. 1)}$$

where T_{ga} and T_{gb} are the glass transition temperatures of the two components of the mixture in degrees Kelvin, and W_a and W_b are their respective weight fractions. For the phenobarbital–citric acid glass system, the observed T_g values were lower than those predicted (Fig. 4), probably because the bonding between citric acid and phenobarbital molecules is less than that between either citric acid or phenobarbital molecules alone.

A thermogram of 1:1 bulk-prepared phenobarbital–citric acid melt (Fig. 5) resembled that for bulk-prepared citric acid melt (Fig. 1). As in that case, the exotherm was attributed to crystallization, and the endotherm was attributed to melting of the crystallized solid. No difference from the *in situ* T_g was observed.

The phenobarbital–citric acid mixture melting temperatures are shown in Fig. 7. As with the benzoic acid–citric acid system, the results obtained by the capillary tube method were in good agreement with those obtained using the differential scanning calorimeter. At compositions below 70% (w/w) phenobarbital, a single sharp endotherm was observed by differential scanning calorimetry. At 70% (w/w) phenobarbital and above, two endothermic peaks were observed in the thermogram. This finding indicates that the phenobarbital was dissolving in the molten citric acid. A second endothermic peak became visible in the thermogram only when the phenobarbital reached its solubility limit in the molten citric acid. The appearance of the second endothermic peak corresponded with the instability of the ≥70% (w/w) phenobarbital glass systems to tempera-

tures above the T_g. Thermograms of these systems showed an exotherm followed by an endotherm, indicating crystallization followed by melting.

Citric acid and phenobarbital seem to form glass solutions rather than dispersions as in the case of citric acid and benzoic acid. Visual examination of the melts of citric acid and phenobarbital mixtures in a capillary tube, under a hot-stage microscope[11], and during bulk preparation showed them to be a single homogeneous phase.

The *in situ* procedure is useful for screening potential glass-forming materials and glass-forming drug–carrier combinations. Physical mixture and solidified melt thermograms and the T_g data indicate whether a drug–carrier mixture will form a glass solution or suspension and what optimum drug–carrier combination can be obtained. In systems that exhibit mechanical and/or thermal instability or that have a T_g below or only slightly above room temperature, the material would not be rigid enough to withstand normal handling operations and could be eliminated from further investigation.

Of particular interest would be the preparation of glass systems containing large quantities of drugs. For example, it might be possible to stabilize the glassy state of a glass-forming drug by mixing it with a small amount of a compatible inert glassy carrier. This procedure would permit the use of less carrier, thereby reducing bulk volume, and aid in the formulation of glass dispersion systems into solid dosage forms.

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[11] Leitz Orthblux microscope equipped with a model 350 heating stage, E. Leitz, Inc., New York, N.Y.

ACKNOWLEDGMENTS

Appreciation is expressed to the Gillette Co. of Boston, Mass., for a fellowship to R. J. Timko.

Paired-Ion Reversed-Phase High-Pressure Liquid Chromatographic Assay of Pentobarbital–Pyrilamine Suppositories

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Received July 17, 1978, from the *School of Pharmacy, Oregon State University, Corvallis, OR 97331.* Accepted for publication October 23, 1978.

Abstract □ The assay of suppositories containing pentobarbital and/or pyrilamine in a water-soluble polyethylene glycol base by high-pressure liquid chromatography is described. No extraction is required. The suppository is dissolved in the mobile phase. This solution is diluted with an internal standard stock solution containing phenobarbital. Chromatographic conditions include a C_{18} bonded microporous silica column and a mobile phase of 65% 4×10^{-3} *M* *n*-butyl sodium sulfonate in 1% acetic acid and 35% acetonitrile. The procedure using commercial products gave results comparable to those obtained by GLC.

Keyphrases □ Pentobarbital–pyrilamine suppositories—analysis, paired-ion reversed-phase high-pressure liquid chromatography, compared to GLC □ Suppositories, pentobarbital–pyrilamine—analysis, paired-ion reversed-phase high-pressure liquid chromatography, compared to GLC □ High-pressure liquid chromatography—analysis, pentobarbital–pyrilamine suppositories, compared to GLC

A pharmacokinetic study involving suppositories containing pentobarbital and/or pyrilamine maleate required in-house manufacturing. This need led to the development of an assay for accurately determining the drug content and uniformity in each lot of suppositories. The rapid high-pressure liquid chromatographic (HPLC) procedure was verified by GLC using commercial products.

Several GLC assays for barbiturates (1–3) and antihistamines (4–7) have been published. In each, appropriate extraction procedures must be carried out to separate the acidic barbiturate from the basic antihistamine. Because the suppositories were made using a water-soluble polyethylene glycol base, reversed-phase HPLC seemed to be the logical approach.

EXPERIMENTAL

Reagents and Chemicals—Authentic samples of pentobarbital sodium[1], pyrilamine maleate[1], phenobarbital[2], propylparaben[1], and

[1] City Chemical.
[2] Mallinckrodt.

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