

Figure 5—Monolayer compression-relaxation isotherms generated by dinoprost butyrate, propionate, and acetate esters on 0.01 M HCl subphase at 25° and $v_0 = 5.17 \text{ \AA}^2/\text{molecule}\cdot\text{min}$.

significant surface pressure reduction, in contrast to the palmitate and decanoate. Another effect of chain length on the stability of these monolayers is seen in the maximum surface pressure developed during compression. The area per molecule at which compression is terminated in Fig. 4 is not a collapse area. Indeed, no collapse is observed for either film. However, under similar conditions of spreading, elapsed time before compression, and compression rate, the hexanoate film is the more stable, as evidenced by the higher surface pressure development throughout the compression sequence. At $32 \text{ \AA}^2/\text{molecule}$, where compression is terminated, the hexanoate film exhibits a maximum pressure of 35 dynes/cm compared to 26.5 dynes/cm for the valerate. The lower pressure of the valerate as well as the surface pressure reduction observed during the noncompression period can be attributed to the shorter chain length and faster dissolution rate from the interface. The hexanoate film is also somewhat soluble in the subphase but to a lesser degree.

Figure 5 presents monolayer behavior for three other members of this alkyl derivative series, butyrate, propionate, and acetate. All three esters tend to accentuate the film behavior previously observed with the hexanoate and valerate films. Monolayer stability is progressively decreased with decreasing alkyl chain length, as evidenced by reductions in surface pressure development during compression. All three compounds exhibit relaxation of surface pressure during noncompression, which appears to be tied directly to their decreased stability as a result of dissolution.

Effect of Primidone Concentration on Glass Transition Temperature and Dissolution of Solid Dispersion Systems Containing Primidone and Citric Acid

M. P. SUMMERS* and R. P. ENEVER

Abstract □ The glass transition temperatures of glasses containing various concentrations of primidone in citric acid were measured and found to increase as the primidone concentration increased. Dissolution studies of these systems and particle-size measurements of primidone precipitated during dissolution of devitrified glasses suggest that the increase in the dissolution rate of the devitrified systems is due to both the small size of the precipitated crystals and the excellent wettability of these systems.

Keyphrases □ Primidone—solid dispersion systems with citric acid,

The use of citric acid as a water-soluble carrier for sparingly soluble drugs was first investigated by Chiou and Riegelman (1). Recently, a study of a solid dispersion system containing primidone in citric acid was reported (2). The systems were prepared by fusing citric acid with primidone; immediately after preparation, they existed in the vitreous state. Both the viscosity of these glasses and

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* To whom inquiries should be directed. Present address: Lederle Laboratories, Pearl River, NY 10965.

effect of concentration on glass transition temperature and dissolution □ Citric acid—solid dispersion systems with primidone, effect of primidone concentration on glass transition temperature and dissolution □ Glass transition temperature—primidone—citric acid solid dispersion systems, effect of primidone concentration □ Dissolution—primidone—citric acid solid dispersion systems, effect of primidone concentration □ Solid dispersion systems—primidone—citric acid, effect of primidone concentration on glass transition temperature and dissolution □ Anticonvulsants—primidone, solid dispersion systems with citric acid, effect of concentration on glass transition temperature and dissolution

their devitrification rate were dependent on the primidone concentration.

Dissolution studies conducted on the devitrified dispersions showed that they dissolved more rapidly than physical mixtures of primidone and citric acid. It was postulated that there was rapid depletion of citric acid from the solid dispersions, leaving a suspension of primi-

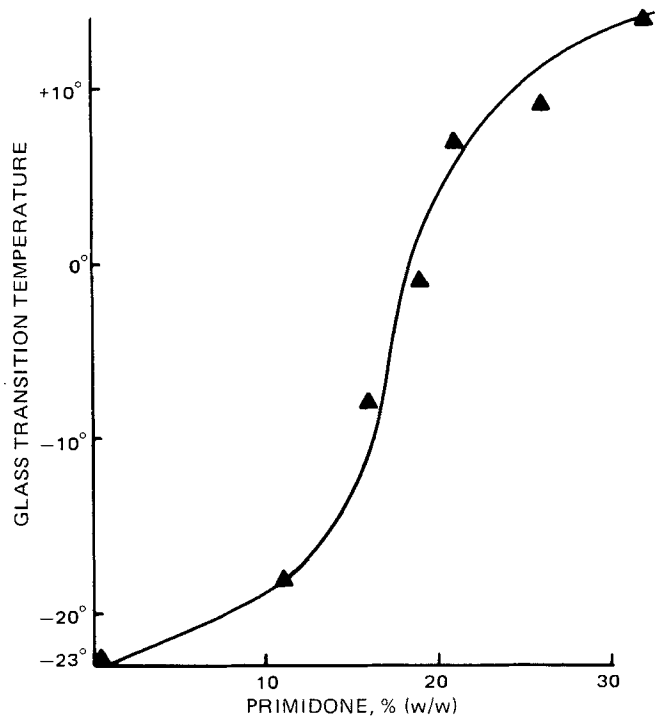


Figure 1—Variation of the glass transition temperature with primidone concentration.

done crystals. The enhanced dissolution rate would then be due, in part, to the small size of these crystals.

The work now reported was conducted to examine the viscous nature of the glasses and to assess the importance of particle size of the precipitated primidone crystals on the dissolution rate of the devitrified systems.

EXPERIMENTAL

Solid Dispersion Systems—The method of preparation was described previously (2).

Glass Transition Temperatures—The glass transition temperatures, T_g , of the vitreous state of the dispersions were measured using a differential scanning calorimeter¹. A marked shift in the baseline due to a change in the specific heat of the material indicated the transition.

Dispersions containing various concentrations of primidone in citric acid were prepared and poured directly into aluminum sample pans. An aluminum cover was placed on the sample before transferring the pan to the sample holder of the instrument. The sample holder was covered with the low temperature head containing liquid nitrogen to obtain starting temperatures of approximately -20° . A heating rate of $2^\circ/\text{min}$ was used, and at least three determinations were performed on each system studied. The precision of the measurement was $\pm 1^\circ$.

Isolation of Primidone Precipitated from Vitreous and Devitrified Dispersions—A 10-g sample of vitreous dispersion containing 16% (w/w) primidone was added to 100 ml of distilled water and shaken until the citric acid dissolved. The resulting suspension of primidone crystals was collected by filtering through a $0.45\text{-}\mu\text{m}$ membrane filter². The crystals were subsequently dried at 50° overnight.

The process was repeated using 10 g of devitrified dispersion containing 16% (w/w) primidone.

The crystallinity and polymorphic form of the precipitated material were checked by X-ray diffraction³ (2).

Dissolution Studies—Dissolution studies were performed on powdered material using the apparatus and methods previously described (2). The dissolution of $150\text{--}250\text{-}\mu\text{m}$ size samples of the following devitrified dispersions in distilled water at 37° was studied: (a) 700 mg of a

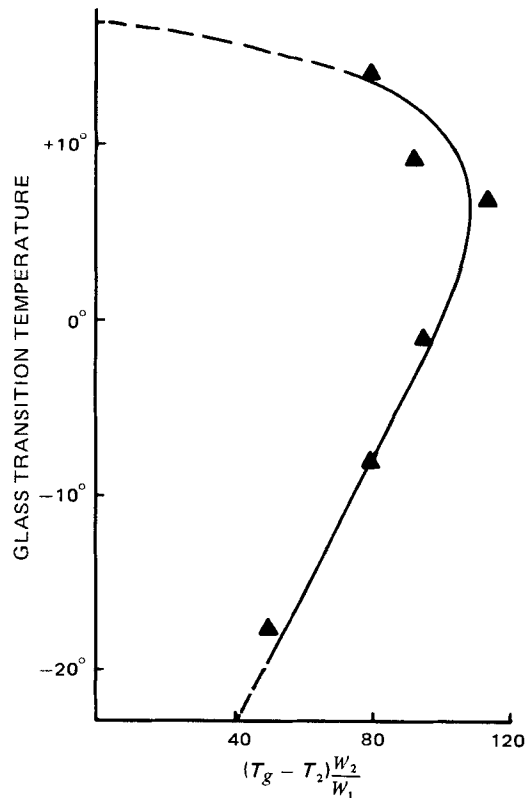


Figure 2—Plot of the glass transition temperature against $(T_g - T_2)W_2/W_1$.

dispersion containing 3% (w/w) primidone (21 mg of primidone), (b) 100 mg of a dispersion containing 21% (w/w) primidone (21 mg of primidone), (c) 200 mg of a dispersion containing 16% (w/w) primidone (32 mg of primidone), and (d) 400 mg of a dispersion containing 8% (w/w) primidone (32 mg of primidone).

The dissolution of physical mixtures produced by adding $150\text{--}250\text{-}\mu\text{m}$ size citric acid crystals to the precipitated primidone was also studied by using 200 mg of mixtures containing 16% (w/w) primidone.

Particle-Size Measurement of Primidone—The size distributions of the commercial primidone starting material and the primidone precipitated from the vitreous and devitrified dispersion systems were measured using an automated particle counter⁴ fitted with a $50\text{-}\mu\text{m}$ orifice tube. The electrolyte was 0.9% (w/w) sodium chloride previously saturated with primidone at room temperature. The solution was filtered before use through a $0.45\text{-}\mu\text{m}$ membrane filter². Two samples of each system were used, and two determinations were performed on each.

RESULTS AND DISCUSSION

Glass Transition Temperature of Vitreous State—The glass transition temperature may be defined as the temperature at which changes in physical properties such as specific heat and viscosity occur that indicate that the vitreous state is changing to the liquid state. Because of the differing bond lengths and bond strengths in the random structure, the point is ill defined (3, 4).

For a series of glasses containing the same constituents, at a fixed temperature above the transition points of all glasses, the glasses possessing the lowest transition temperatures will be the least viscous. Previous work with primidone-citric acid dispersions showed that the devitrification rate of the systems was dependent upon the primidone concentration and that the most rapidly devitrifying systems were the least viscous (2). The present glass transition data confirm this relationship. As Fig. 1 shows, the smaller the primidone concentration, the lower was the glass transition temperature and hence the lower was the viscosity of the system at ambient temperature.

The glass transition points of all dispersions were below ambient temperature (20°). Therefore, these systems, which previously were re-

¹ Perkin-Elmer DSC-1B, Perkin-Elmer, Beaconsfield, Bucks, United Kingdom.

² Oxoid Ltd., London, United Kingdom.

³ Nonius Mk2 self-focusing Guinier diffractometer.

⁴ Model A Coulter counter, Coulter Electronics Ltd., Dunstable, United Kingdom.

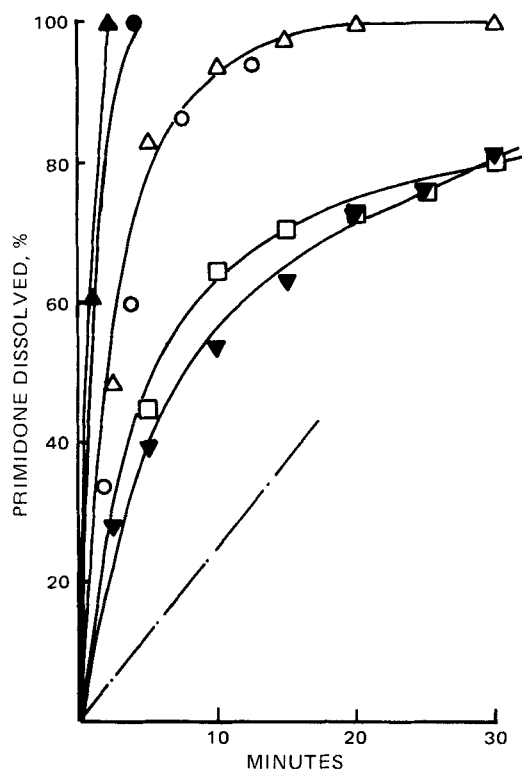


Figure 3—Dissolution rate of primidone. Key: ▲, 3% (w/w) devitrified system; ●, 8% (w/w) devitrified system; △, 16% (w/w) devitrified system; ○, 21% (w/w) devitrified system; ▼, primidone from 16% (w/w) devitrified system (physical mixture); □, primidone from 16% (w/w) vitreous system (physical mixture); and — · —, 16% physical mixtures previously tested (2), primidone particle size of 150–250 μm .

ferred to as glasses, are more correctly described as highly viscous supercooled liquids.

Gordon and Taylor (5) derived an equation to predict the variation of the glass transition temperature with composition for a copolymer system:

$$T_g = -k(T_g - T_2) \frac{W_2}{W_1} + T_1 \quad (\text{Eq. 1})$$

where T_1 and T_2 are the glass transition temperatures of pure Components 1 and 2, W_1 and W_2 are the weight fractions of the components, and k is a coefficient defined by:

$$k = \Delta B_1 / \Delta B_2 \quad (\text{Eq. 2})$$

where ΔB is the difference between the coefficients of expansion of the vitreous and liquid states.

Equation 1 is valid provided the following relationship is obeyed (6):

$$A_{AB} = \frac{A_{AA} + A_{BB}}{2} \quad (\text{Eq. 3})$$

where A_{AA} and A_{BB} are the bonding energies between molecules of the individual components, and A_{AB} is the bonding energy between molecules in the mixture.

Figure 2 shows a plot of the citric acid–primidone data in accordance with Eq. 1. Since the graph is not a straight line, the system does not obey the ideal situation described by Eq. 1. Similar cases have been shown for copolymer systems (6). The bonding energy between citric acid and primidone molecules is not the arithmetic mean of the bonding energies of the pure components and may support the hypothesis previously advanced (2) that the concentration-dependent devitrification of these systems could be due to extensive formation of strong hydrogen bonds between the component molecules in the vitreous state.

Dissolution Studies of Devitrified Systems Containing Low Primidone Concentrations—Figure 3 shows a plot of the percentage primidone released against time for systems containing 3, 8, 16, and 21% (w/w) primidone. The dissolution profiles of the 16 and 21% (w/w) devitrified systems are the same as those previously published (2) and indicate that the percentage primidone released is independent of the

Table I—Particle-Size Data of Primidone Crystals

Source of Crystals	Mean Particle Diameter, μm	SD
3% (w/w) devitrified glass	5.2 ± 0.3	2.10
8% (w/w) devitrified glass	4.6 ± 0.2	1.91
16% (w/w) devitrified glass	4.7 ± 0.3	2.06
21% (w/w) devitrified glass	4.7 ± 0.3	1.91
32% (w/w) devitrified glass	4.5 ± 0.3	1.92
16% (w/w) glass	4.2 ± 0.2	1.95
Commercial material	6.2 ± 0.4	2.17

primidone content of the sample. However, the 3 and 8% (w/w) primidone systems do not follow this pattern, even though the quantities of primidone in the samples are equivalent to those in the 21 and 16% (w/w) systems, respectively.

Particle-Size Measurement of Precipitated Crystals—Table I shows the mean particle diameter of primidone precipitated from the solid dispersion systems, together with values for the standard deviations of the log-normal distributions. Prior to particle-size measurement, the crystals were well dispersed with an octylphenol–ethylene oxide polymer⁵ so measurements were conducted on a suspension of individual particles.

The mean diameter and size distribution of the precipitated crystals did not vary significantly between systems containing different concentrations of primidone. The mean diameter of the commercial sample was, however, slightly larger than that of the precipitated crystals.

Dissolution Studies of Physical Mixtures of Precipitated Primidone and Citric Acid—The results of the dissolution studies of 16% (w/w) physical mixtures of primidone precipitated from the dispersion before and after devitrification are shown in Fig. 3. X-Ray diffraction studies confirmed that the precipitate was the crystalline Form II primidone polymorph. The data in Fig. 3 indicate that the smaller particle size of the primidone in these mixtures was responsible for an increased dissolution rate when compared with physical mixtures previously tested (containing primidone of 152–250- μm size) (2). The dissolution rates,

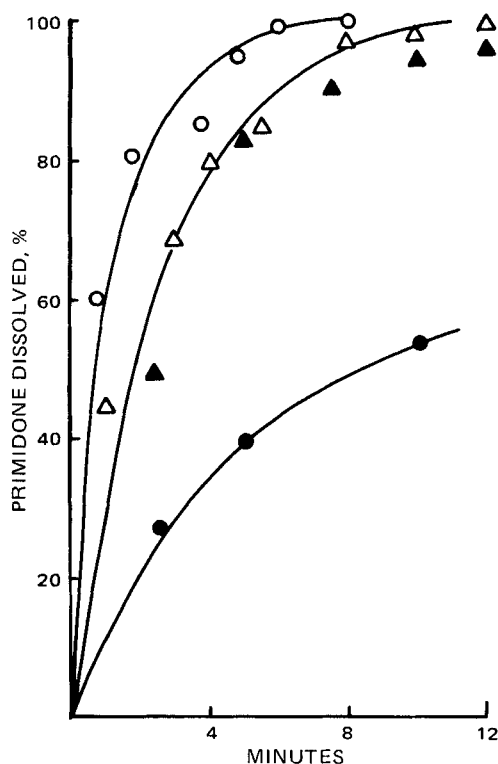


Figure 4—Effect of dispersal with polyethylene glycol 300 on the dissolution rate of primidone. Key: ○, 16% (w/w) physical mixture (dispersed); ●, 16% (w/w) physical mixture (not dispersed); △, 16% (w/w) devitrified system (dispersed); and ▲, 16% (w/w) devitrified system (not dispersed).

⁵ Nonidet P40, British Drug Houses, Poole, Dorset, United Kingdom.

however, were not as rapid as those from the 16% (w/w) devitrified dispersion.

It is doubtful whether the increased solubility of primidone in the citric acid contained in the diffusion layer surrounding the dissolving devitrified dispersion could account for the differences in dissolution of the physical mixture and the devitrified dispersion. If it is assumed that the diffusion layer thickness is about 3×10^{-3} cm (7) and that the diffusion layer is saturated with citric acid, then calculations indicate that the maximum amount of primidone that could be in solution is 1–10% of the primidone content of the system (depending upon the primidone concentration in the dispersion). Thus, a gross excess of primidone is present in all cases.

The precipitated primidone crystals were very cohesive, and incomplete wetting could have inhibited dissolution from the physical mixtures. To test this possibility, the dissolution experiment was repeated using another 200-mg sample of the 16% (w/w) physical mixture of precipitated primidone and citric acid previously dispersed with 0.4 ml of polyethylene glycol 300⁶. A sample of the 16% (w/w) devitrified dispersion was also examined in the same manner. From the results (Fig. 4), it can be seen that the dissolution of the devitrified dispersion was not significantly affected by the addition of the polyethylene glycol. The dissolution of the physical mixture was, however, increased and was greater than that of the devitrified dispersion, even though complete dispersal of the mixture was not achieved.

These results indicate that the primidone particles precipitated during dissolution of the devitrified system remain as loose agglomerates during the dissolution process. The collection of these particles and their re-dispersal with polyethylene glycol in the mixture with citric acid probably result in the destruction of these agglomerates to produce individual particles. The resulting increase in the primidone surface area is responsible for the higher dissolution rate seen with these physical mixtures.

The enhanced dissolution rate of primidone in these devitrified systems (2) is thus confirmed to be due to the reduction in particle size of the primidone in the system and the improved wetting characteristics of the solid dispersion system. Nevertheless, the dissolution rate is impaired by the failure of the precipitated primidone particles to separate com-

pletely during dissolution. The enhanced dissolution rates of the 3 and 8% (w/w) devitrified glasses could be due to better particle separation during dissolution.

CONCLUSIONS

Interactions between primidone and citric acid occur when they are fused together, and viscous supercooled liquids are produced when the melt is cooled. The viscosity of the supercooled liquids increases with increasing primidone concentration, as reflected in an increased glass transition temperature.

During dissolution of the devitrified systems, primidone is precipitated in aggregates of fine particles. The relatively large surface area produced by this process results in the powdered devitrified dispersions (150–250- μ m size) having a faster rate of dissolution than physical mixtures of primidone and citric acid of the same size.

The aggregation of primidone particles during dissolution appears to be dependent on the primidone concentration in the dispersion. At low concentrations (3% w/w), the aggregation is less than at 8–16% (w/w), resulting in a faster dissolution of primidone from the devitrified dispersion.

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* To whom inquiries should be directed.

⁶ Koch Light Laboratories, Colnbrook, Bucks, United Kingdom.

Phytochemical Investigation of Xanthonones of *Eustoma grandiflorum* (Raf.) Shinnery

GERALD SULLIVAN^x, FRANCIS D. STILES, and KARL-HEINZ A. ROSLER*

Abstract □ Six polyoxygenated xanthonones were isolated from the roots of *Eustoma grandiflorum* (Raf.) Shinnery collected in Texas. Structural elucidation of five of these xanthonones (1-hydroxy-3,7-dimethoxyxanthone, 1-hydroxy-3,5-dimethoxyxanthone, 1-hydroxy-3,5,6,7-tetramethoxyxanthone, 1-hydroxy-3,5,6,7,8-pentamethoxyxanthone, and 1-hydroxy-3,7,8-trimethoxyxanthone) was accomplished via UV, IR, NMR, and mass spectrometry; traditional physical-chemical methods; or direct comparison with a prepared derivative. The sixth xanthone derivative was characterized incompletely. The pentamethoxyxanthone

is a new compound and has been designated generically as eustomin. The probable occurrence of these six xanthone compounds in the plant as glycosides is reported.

Keyphrases □ *Eustoma grandiflorum*—methanol extract of roots, six polyoxygenated xanthonones isolated □ Xanthonones, polyoxygenated—six isolated from methanol extract of roots of *Eustoma grandiflorum* □ Hydroxyxanthonones—six isolated from methanol extract of roots of *Eustoma grandiflorum*

Eustoma grandiflorum (Raf.) Shinnery (Gentianaceae), a plant primarily indigenous to the southwestern portion of the United States, is commonly referred to as the catchfly-gentian, Texas bluebell, and lira de San Pedro. It has a very showy, eye-catching flower, blooming in great profusion in several areas of Texas. A prominent taproot

is evident, and even a cursory examination reveals a bright yellow pigment.

The Gentianaceae family is known to produce xanthone derivatives liberally, and several have been isolated from related genera such as *Canscora*, *Frasera*, *Gentiana*, and *Swertia* (1–5). Plant extracts obtained from these genera