Phase Behavior of Binary and Ternary Amorphous Mixtures Containing Indomethacin, Citric Acid, and PVP

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Purpose. To better understand the nature of drug-excipient interactions we have studied the phase behavior of amorphous binary and ternary mixtures of citric acid, indomethacin and PVP, as model systems.

Methods. We have prepared amorphous mixtures by co-melting or coprecipitation from solvents, and have measured glass transition temperatures with differential scanning calorimetry.

Results. Citric acid and indomethacin in the amorphous state are miscible up to 0.25 weight fraction of citric acid, equivalent to about 2 moles of citric acid and 3 moles of indomethacin. Phase separation, as reflected by two Tg values, occurs without crystallization leading to a saturated citric acid-indomethacin amorphous phase and one essentially containing only citric acid. PVP-citric acid and PVP-indomethacin form non-ideal miscible systems at all compositions. A ternary system containing 0.3 weight fraction of PVP produces a completely miscible system at all citric acid-indomethacin compositions. The use of 0.2 weight fraction of PVP, however, only produces miscibility up to a weight fraction of 0.4 citric acid relative to indomethacin. The two phases above this point appear to contain citric acid in PVP and citric acid in indomethacin, respectively.

Conclusions. Two components of an amorphous solid mixture containing citric acid and indomethacin with limited solid state miscibility can be solublized as an amorphous solid phase by the addition of moderate levels of PVP.

KEY WORDS: glass transition temperature; different scanning calorimetry; amorphous; phase separation; miscibility.

INTRODUCTION

Previous studies in this laboratory have been directed toward an understanding of the amorphous solid state and its role in affecting various physical and chemical properties in pharmaceutical systems (1,2). To date emphasis in our work has been on single component systems (3,4) and some binary systems, including small molecule-polymer mixtures (5,6) and those containing water as one of the components (7). In this study, we have selected as model systems three materials, citric acid, indomethacin and polyvinylpyrrolidone (PVP), which we have studied previously as single components (3,4,8). Through the measurement of the glass transition temperatures of their binary and ternary systems, we have evaluated their tendency to form miscible or immiscible amorphous solid state solutions. Such information, we believe, should be helpful in establishing a better understanding of drug-excipient interactions in systems containing small and large molecules in the amorphous state.

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MATERIALS

Crystalline anhydrous citric acid (J. T. Baker Chemical Co.) and the γ crystalline form of indomethacin (1-[p-chlorobenzoyl]-5-methoxy-2-methylindole-3-acetic acid, Sigma) were used without further treatment. PVP (polyvinylpyrrolidone) K90 (ISP) was dried at 105°C in a vacuum oven (~ 100 m Torr) for 12 hours before the preparation of mixtures.

Citric acid-indomethacin binary mixtures were prepared by co-melting at 155°C and quench-cooling various ratios of citric acid and indomethacin both *in situ* in DSC pans and in large quantities (bulk). Bulk samples were then stored until use over phosphorous pentoxide in a desiccator at −20°C.

Mixtures of PVP-citric acid and PVP-citric acid-indomethacin were prepared by using a solvent evaporation technique in a manner similar to that used to prepare PVP-indomethacin mixtures in previous studies (5,9). Appropriate amounts of PVP, citric acid and indomethacin were dissolved in 100 ml of anhydrous methanol at 65°C. The solvent was removed by using a rotary evaporator held at appropriate temperatures. The coprecipitates were dried in a vacuum oven at room temperature for 24 hours, and then stored in a desiccator at −20°C and 0% RH.

METHODS

Thermal Analysis

Differential Scanning Calorimetry (DSC) measurements were performed using a Seiko SSC 220/5200 DSC (Seiko Instruments). Dry nitrogen was used as the purge gas and liquid nitrogen as the coolant. High purity indium, gallium and mercury were used for temperature calibration. Samples (5–15 mg) were carefully weighed into aluminum pans in the glove box under nitrogen flow. During measurements, aluminum pans were exposed to the atmosphere through a pinhole in the lid.

In order to minimize the effect of thermal history caused by different preparation methods before the measurements of Tg, all amorphous mixtures were heated in DSC pans to 155°C and then cooled down to −60°C by a liquid nitrogen cooling accessory at ~30K/min, and the subsequent heating scans were recorded. The values of Tg represent the onset temperature for the characteristic heat capacity change obtained at a scanning rate of 10K/min. All reported values are the average of at least three independent measurements.

X-Ray Powder Diffraction

All X-ray powder diffraction patterns were collected by utilizing a Scintag PadV X-ray diffractomer (Scintag Inc.). The radiation was generated by a copper Kα filter at 35 kV and 40 mA. The samples were placed in a quartz sample holder and scanned from 10 to 50 degrees at a scanning rate of 5 2θ degree/min. All samples revealed the halo characteristic of an amorphous phase.

RESULTS

Citric Acid-Indomethacin Binary Mixtures

Figure 1 shows DSC curves of citric acid-indomethacin mixtures at 0.1 and 0.5 weight fraction of citric acid, respec-

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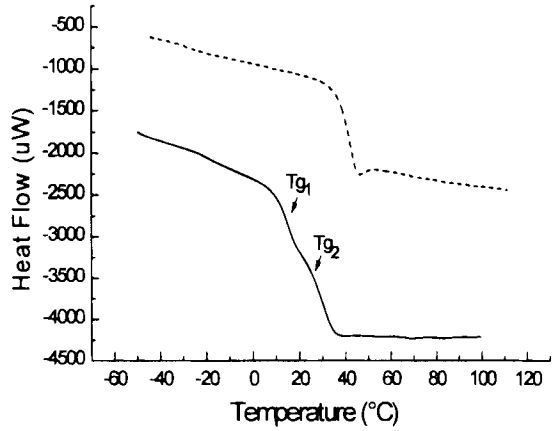

Fig. 1. DSC curves of citric acid-indomethacin binary mixtures which contain 0.1 (···) and 0.5 (—) weight fraction of citric acid, respectively. Tg_1 and Tg_2 indicate the corresponding values discussed in the text.

tively. It demonstrates one glass transition for the mixture at 0.1 weight fraction of citric acid, indicating that citric acid and indomethacin are miscible in the amorphous state at this composition. At 0.5 weight fraction of citric acid, two glass transitions were observed, indicating that phase separation of two amorphous phases has likely occurred. The values of Tg over the entire composition range of citric acid-indomethacin are summarized in Fig. 2. Up to 0.25 weight fraction of citric acid there is only one Tg and it decreases with citric acid concentration. Since citric acid has a Tg of 11°C (3) and indomethacin 42°C (4), a single Tg intermediate to these values is expected for such a miscible system. Above 0.25 weight fraction of citric acid, there are two Tg values, which we designate as Tg_1 and Tg_2. As can be seen in Fig. 2, as the citric acid content is raised, the higher Tg, Tg_2 is slightly reduced. The values of Tg_1, the lower Tg, are independent of composition and maintain the same value as that of pure citric acid. The values obtained from the *in situ* and selected bulk samples are in excellent agreement.

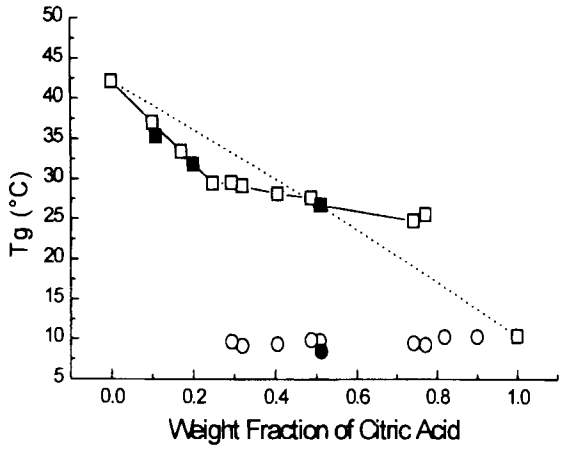

Fig. 2. Values of Tg for binary mixtures of citric acid-indomethacin as a function of weight fraction of citric acid. The square symbols correspond to the values of Tg_2, while the circles show that of Tg_1. Open symbols are the results obtained from *in situ* samples and filled ones are from bulk samples. The dotted line (···) represents the predictions based on the Gordon-Taylor equation (equation 1 in the text).

PVP-Citric Acid and PVP-Indomethacin Mixtures

Over the entire composition range, PVP and citric acid appear to be miscible with only one Tg, as shown in Fig. 3a. For later comparison, the curve for PVP-indomethacin obtained under the same conditions in earlier studies (9) is presented in Fig. 3b. Again, we see one Tg, indicating miscibility.

PVP-Citric Acid-Indomethacin Ternary Mixtures

To begin to probe the effects of adding a third component, PVP, to a binary system showing limited miscibility, we initially chose to examine systems that contained PVP at 0.2 and 0.3 weight fraction of the total sample weight. Such levels had previously been shown to be excellent inhibitors of crystallization of indomethacin (9) and sucrose (6). In Tables 1 and 2, we report the Tg values along with the actual weight fraction compositions of citric acid, indomethacin and PVP for the 0.3 and 0.2 weight fraction of PVP systems, respectively. To later relate these data to those in Fig. 2, in Figs. 4a and 4b we have plotted the Tg of the ternary systems against the weight fraction of citric acid, expressed as weight of citric acid divided by the sum of the weights of indomethacin and citric acid, as in Fig. 2. It can be seen that at all weight fractions of citric acid, in

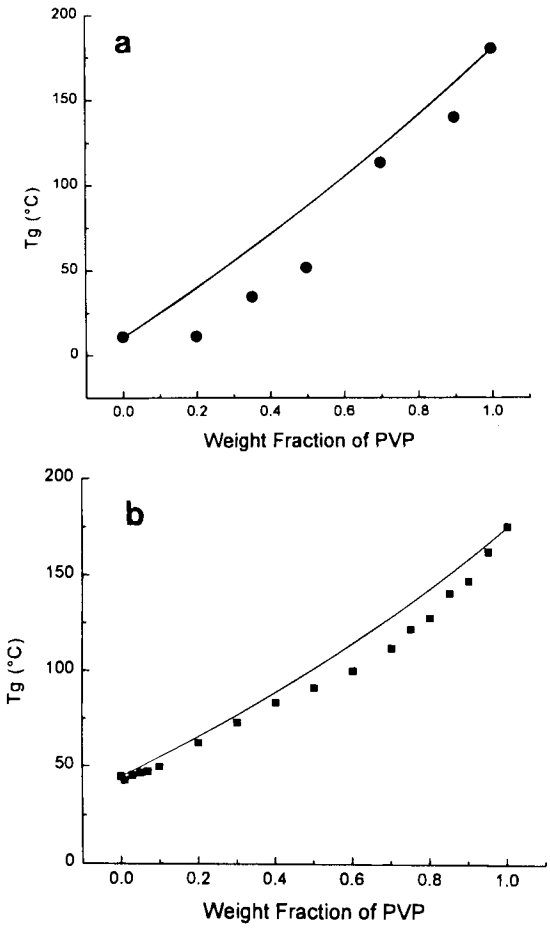

Fig. 3. Values of Tg for binary mixtures of PVP-citric acid (a) and PVP-indomethacin (b) as a function of PVP content. The lines show the predicted values from the Gordon-Taylor equation (equation 1 in the text).

Table 1. Tg Values of PVP-Citric Acid (CA) -Indomethacin (IM) Mixtures Containing 0.3 Weight Fraction of PVP as a Function of Citric Acid and Indomethacin Weight Fraction

Composition			
W_{PVP}	W_{CA}	W_{IM}	Tg(°C)
0.3	0.14	0.56	63.0(0.3)[a]
0.3	0.28	0.42	52.0(0.9)
0.3	0.35	0.35	46.4(1.2)
0.3	0.42	0.28	42.0(0.8)
0.3	0.49	0.21	36.8(2.7)
0.3	0.56	0.14	27.2(0.3)
0.3	0.63	0.07	23.1(2.8)

[a] The numbers in parenthesis represent the standard deviation.

the presence of 0.3 weight fraction of PVP, only one Tg is observed, indicating complete miscibility of citric acid and indomethacin in PVP over the entire concentration range. Also we can note that citric acid reduces Tg significantly from the value of 0.3 weight fraction of PVP in indomethacin, as its concentration increases. In Fig. 4b, we see in the presence of 0.2 weight fraction of PVP one Tg value with increasing citric acid up to a weight fraction of citric acid to indomethacin 0.4, followed by two Tg values. Here, Tg_1 represents the lower Tg and Tg_2 represents the higher Tg. This miscibility limit of 0.4 weight fraction of citric acid in indomethacin can be directly compared to the 0.25 weight fraction values shown in the absence of PVP.

DISCUSSION

Binary Systems

Up to 0.25 weight fraction of citric acid, citric acid and indomethacin are miscible primarily due to the hydrogen bonds that can occur between the carboxylic acid groups and hydroxyl group provided by individual components. Beyond the miscibility limit, the fixed values of Tg_1 (~11°C) indicate the existence of a separated citric acid amorphous phase. Though Tg_2 shows a slight reduction with increasing citric acid, we can presume that it represents close to a "saturated" citric acid-indomethacin amorphous phase at these higher compositions, i.e., maximum amount of citric acid molecularly dispersed in indomethacin as an amorphous mixture.

Table 2. Tg Values of PVP-Citric Acid (CA)-Indomethacin (IM) Mixtures Containing 0.2 Weight Fraction of PVP as a Function of Citric Acid and Indomethacin Weight Fraction

Composition				
W_{PVP}	W_{CA}	W_{IM}	Tg_2(°C)	Tg_1(°C)
0.2	0.13	0.67		47.8(0.8)[a]
0.2	0.24	0.56		42.2(1.1)
0.2	0.32	0.48		34.7(0.2)
0.2	0.36	0.44	46.8(0.7)	29.2(0.4)
0.2	0.40	.40	42.8(2.9)	25.3(1.3)
0.2	0.48	0.32	37.9(3.8)	25.2(0.7)

[a] The numbers in parenthesis represent the standard deviation.

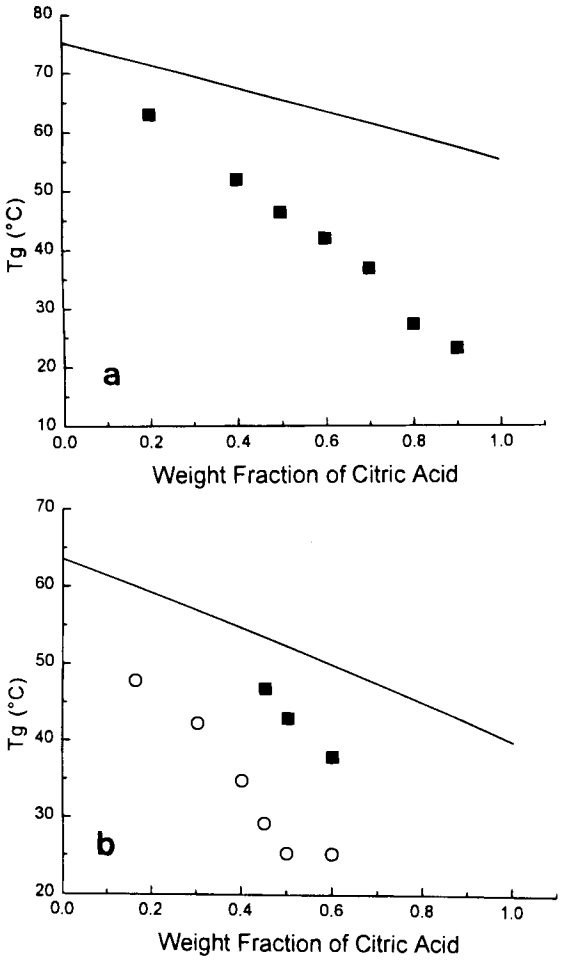

Fig. 4. Values of Tg for ternary mixtures of PVP-citric acid-indomethacin containing 0.3 weight fraction (a) and 0.2 weight fraction (b) of PVP as a function of weight fraction of citric acid relative to weight of indomethacin plus citric acid. Lines represent the predictions based on the extended Gordon-Taylor equation (equation 3 in the text). In Figure 4b, The symbols (○) and (■) correspond to the values of Tg_1 and Tg_2, respectively.

Since citric acid has a lower Tg than indomethacin, i.e. 11°C and 42 °C, respectively, we would expect the Tg of their mixtures to be intermediate between these values with citric acid acting to plasticize indomethacin. Likewise, since PVP has a Tg of 177°C, we would expect binary miscible systems with PVP containing either citric acid or indomethacin to exhibit higher Tg values than those observed for these individual components. To assess the extent to which such mixtures might exhibit ideal or non-ideal mixing, we can analyze the various systems using a mixing rule such as expressed in the Gordon-Taylor equation (10).

$$Tg_{12} = \frac{W_1 Tg_1 + KW_2 Tg_2}{W_1 + KW_2} \quad (1)$$

where K may be estimated as (11),

$$K \approx \frac{Tg_1 \rho_1}{Tg_2 \rho_2} \quad (2)$$

and W_1, W_2, Tg_1, Tg_2, ρ_1 and ρ_2 are the weight fraction, glass

transition temperature and density of the amorphous state for each component, respectively.

As seen in Fig. 2, in comparing the Tg values of the miscible citric acid-indomethacin systems, the plasticizing effects of citric acid on indomethacin are greater than predicted from ideal mixing, where free volumes are additive, where there are no strong specific hetero-contacts relative to homo-contacts and no overall excess free energy of mixing (10,12). Such an enhanced plasticizing effect, resulting from a net increase in free volume relative to an ideal mixture, is believed to arise from a greater tendency for interaction between components for themselves than for each other (12,13), with miscibility being maintained by an increase in entropy due to a net loss of hydrogen bonding upon mixing (13,14). Thus, although we have not been able to measure such free volume and thermodynamic quantitites, our results seem consistent with this hypothesis, but not proven.

Upon the addition of 0.25 weight fraction of citric acid, which represents a ratio of about 2 moles of citric acid to 3 moles of indomethacin, the system appears to become "saturated" and citric acid separates as an amorphous phase. The term saturated is used in analogy to a liquid solution where one component exceeds its limit of miscibility in another component and bulk phase separation occurs. Over the time scale of these experiments, we found no evidence for citric acid or indomethacin crystals in these systems from x-ray powder diffraction. Presumably, at this point the self association of citric acid relative to its ability to hydrogen bond with indomethacin becomes significant enough to offset any positive effects due to the entropy of mixing, and therefore an amorphous phase separation occurs. From previous vibrational spectroscopic studies with amorphous indomethacin, it was shown that carboxylic acid dimers exist to a significant extent, and it is these dimer hydrogen bonds that primarily must be broken for indomethacin to hydrogen bond with another component (5). Citric acid with three carboxylic acid groups and one hydroxyl group, likewise, would be expected to show a strong tendency for self association through hydrogen bonding. Unfortunately, we could not isolate large enough quantities of bulk citric acid in the amorphous state and study it with such spectroscopies because of its low Tg.

From our results with the binary systems, PVP-indomethacin and PVP-citric acid, it appears that PVP is capable of hydrogen bonding with these materials to form miscible amorphous systems over the entire composition range. Since PVP only has polar groups capable of donating electrons to a hydrogen bond, it cannot hydrogen bond with itself. From Figures 3a and 3b, we can see that indomethacin and PVP form a miscible mixture, with relatively small deviations from the Gordon-Taylor predictions, whereas citric acid clearly exhibits greater deviations, particularly at low levels of PVP. This tendency for PVP to be less of an antiplasticizer than predicted, and hence exhibit a greater free volume than predicted, has also been observed with the very polar sucrose molecule when mixed with PVP, and has been explained by the strong tendencies for the polar sucrose to strongly self associate through hydrogen bonding offsetting to some extent the contribution of interaction with PVP (6,13).

Ternary Systems

With an ability to disrupt the hydrogen bonding which gives rise to self association of citric acid and indomethacin themselves, one might expect PVP added to a mixture of citric acid and indomethacin to prevent such association enough to enhance their mutual miscibility. To test this idea, we initially chose a ternary mixture in which PVP represents 0.3 weight fraction of the composition, and found complete miscibility, as shown in Table 1 and Fig. 4a. To assess the extent of ideality and nonideality of mixing, we have extended the Gordon-Taylor equation (Eq. 1) to three components as,

$$Tg_{123} = \frac{w_1 Tg_1 + K_1 w_2 Tg_2 + K_2 w_3 Tg_3}{w_1 + K_1 w_2 + K_2 w_3} \quad (3)$$

and

$$K_1 \approx \frac{Tg_1 \rho_1}{Tg_2 \rho_2} \text{ and } K_2 \approx \frac{Tg_1 \rho_1}{Tg_3 \rho_3} \quad (4)$$

As shown in Fig. 4a, the experimentally determined Tg values in this system are significantly lower than might be predicted from an ideal mixture of citric acid, indomethacin and PVP.

To further test the influence of PVP composition on the miscibility of citric acid and indomethacin, we reduced the amount of PVP to a weight fraction of 0.2, and indeed, as shown in Fig. 4b, we found that a distinct "solubility" limit occurred again, but now at the equivalent of 0.4 weight fraction of citric acid to indomethacin rather than 0.25 as with the binary system. Thus, the ability of PVP to solubilize the citric acid-indomethacin mixture in the amorphous state appears to be sensitive to PVP composition, most likely due to the number of hydrogen bonds that can be formed by PVP with each component. Measurement of Tg could not be made above a weight fraction of 0.6 for citric acid-indomethacin because beyond this point a crystalline phase separated out during the preparation of coprecipitated mixtures.

In those cases where two Tg values are observed, we initially might have thought that Tg_2 would represent an amorphous phase rich in indomethacin, while Tg_1 would represent an amorphous phase rich in citric acid. However, as shown in Fig. 5, when we compare our data in Fig. 4b to those obtained in Fig. 2, we can see that the Tg_1 values for PVP-citric acid-indomethacin tend to level off and coincide quite closely to the Tg_2 values of citric acid-indomethacin. Although it was not possible to physically separate these amorphous phases to directly estimate the compositions of various components, we might tentatively conclude that in the ternary system with 0.2 weight fraction of PVP one amorphous phase, represented by Tg_1, is equivalent to the "saturated" mixture of citric acid-indomethacin. Based on this conclusion, we were able to calculate for the ternary system the compositions of the other phase reflected by Tg_2, by assuming that the composition of the "saturated" citric acid-indomethacin phase contains citric acid with a weight fraction of 0.25, and therefore that Tg_2, representing the other phase, only consists of PVP and citric acid. Indeed, as shown in Fig. 6, the three Tg_2 values for the PVP-citric acid-indomethacin system fall almost exactly on the plot of citric acid in PVP without any indomethacin present.

CONCLUSIONS

For either binary or ternary amorphous systems containing indomethacin, citric acid and PVP, where two Tg values appear,

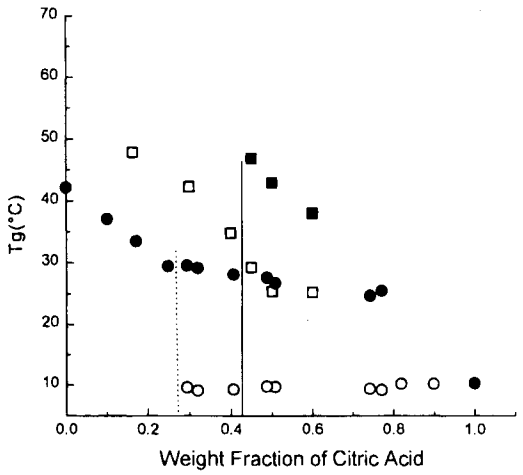

Fig. 5. Comparison of Tg for binary mixtures of citric acid-indomethacin and those for ternary mixtures of PVP-citric acid-indomethacin with 0.2 weight fraction of PVP, as a function of weight fraction of citric acid relative to weight of indomethacin plus citric acid. The circles represent the results of the binary system while the squares represent the ternary system. The open symbols correspond to the values of Tg_1 and the filled ones to those of Tg_2, respectively. The miscibility limits are shown as vertical lines: dotted line (⋮) for the binary system; solid line (|) for the ternary system.

we conclude that phase separation into two amorphous systems occurs without any evidence of crystallization. It appears from the respective Tg values obtained that amorphous citric acid separates from binary amorphous mixtures with indomethacin leaving behind a nearly "saturated" citric acid-in-indomethacin amorphous solution. With the addition of 0.3 weight fraction

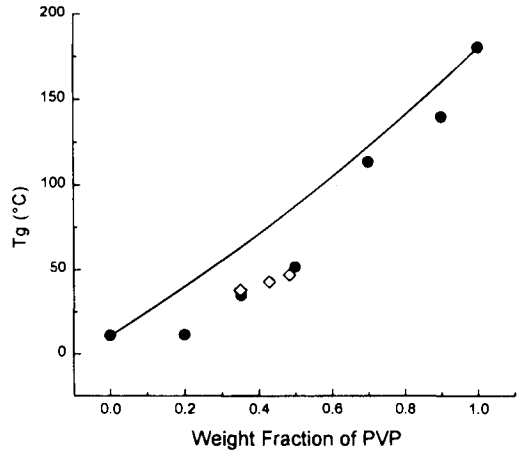

Fig. 6. Values of Tg_2 (◇) for PVP-citric acid-indomethacin containing 0.2 weight fraction of PVP as a function of calculated composition of the separate phase based on the assumption that, above the miscibility limit, the phase reflected by Tg_1 is the "saturated" citric acid-indomethacin phase containing 0.25 weight fraction of citric acid. For comparison, the values of PVP-citric acid (●) are also plotted.

of PVP, citric acid, indomethacin and PVP are miscible at all citric acid-indomethacin compositions. At 0.2 weight fraction of PVP, beyond a certain citric acid-indomethacin composition, phase separation occurs with the formation of what appears to be a nearly "saturated" citric acid-in-indomethacin amorphous phase, and a second amorphous phase consisting of the remaining citric acid solublized in PVP.

Further studies with this and other multicomponent systems over a wider range of conditions should be useful in assessing how complex amorphous mixtures arising during pharmaceutical processing of various solid formulations might be expected to behave with regard to both stability and bioavailability due to varying degrees of miscibility.

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