Neotame Anhydrate Polymorphs II: Quantitation and Relative Physical Stability

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Purpose. To study the relative thermodynamic and kinetic stabilities of neotame anhydrate polymorphs A, D, F, and G, and to develop a quantitative method for analyzing polymorphic mixtures of A and G by powder X-ray diffractometry (PXRD).

Methods. Based on the melting points, heats of fusion, and densities of the four polymorphs, thermodynamic rules were applied to study their thermodynamic relationships. The phase transition temperature of Forms A and G was estimated from their heats of solution and intrinsic dissolution rates (J) in 2-propanol. Using PXRD, a method for the quantitative analysis of polymorphic mixtures of Forms A and G was developed. Binary polymorphic mixtures of Forms A, D, F, or G were stored under zero relative humidity at 23 or 70°C, and their compositions were monitored by PXRD.

Results. The endothermic enthalpy of solution of A, D, F, and G follows the rank order: G (29.71 ± 0.82 kJ/mol, n = 4) > A (28.48 ± 0.51 kJ/mol, n = 4) > D (20.43 ± 0.45 kJ/mol, n = 4) > F (18.77 ± 0.31 kJ/mol, n = 4). The van't Hoff plots of $\ln(J)$ against $1/T$ for A and G show good linearity between 25°C and 32°C. At 23°C polymorphic mixtures remain unchanged for 4 months. However, at 70°C the phase transition is fast and the relative stability of the four polymorphs follows the rank order: G > D > F and G > A.

Conclusions. PXRD provides a reliable and accurate technique for the quantitative analysis of polymorphic mixtures of Forms A and G. Among the four polymorphs, A-G and A-D are enantiotropic pairs, whereas D-F, D-G, F-G are monotropic pairs. The phase transition temperature between A and G lies within the range 35–70°C.

KEY WORDS: enantiotropy; enthalpy of solution; intrinsic dissolution rate; neotame; polymorphism; powder X-ray diffractometry.

INTRODUCTION

Polymorphism is defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice (1). Two types of polymorphism, enantiotropy and monotropy, may be distinguished by examining the free energy relationships of the polymorphs (2–6). A transition from one polymorph to another is designated as enantiotropic, if it can be reversed in the solid state. In this case a transition temperature exists at which the two forms are in equilibrium with each other. If the change from one polymorph to another is irreversible in the solid state, the two forms have a monotropic relationship. In practice, if one polymorph is stable over one range of temperature and pressure and another polymorph is stable over another range of temperature and pressure, the two polymorphs are said to be enantiotropic. On the other hand, if only one polymorph is stable at all temperatures below the melting point, all other polymorphs being unstable or metastable, the system is said to be monotropic. At a given temperature and pressure, the more stable polymorph has the lower Gibbs free energy, G, than the metastable form.

Burger and Ramberger developed and employed the following four thermodynamic rules (a–d) to determine the thermodynamic relationships among different polymorphs (2–4).

(a) *Heat of Transition Rule.* Statistical mechanics shows that the enthalpy curves of two polymorphs of a substance do not intersect, whereas the free energy curves may intersect only once, in the case of enantiotropy, or not at all, in the case for monotropy. If an endothermic transition is observed at some temperature, it may be assumed that there is a transition point below it, i.e., the two forms are related enantiotropically. If an exothermic transition is observed at some temperature, it may be assumed that there is no transition point below it, i.e., the two forms are related monotropically, or the transition point is higher.

(b) *Heat of Fusion Rule.* If the higher melting form has the lower heat of fusion, the two forms are usually enantiotropic, otherwise they are monotropic.

(c) *Density Rule.* If one form of a molecular crystal has a lower density than the other, it may be assumed to be less stable at zero Kelvin.

(d) *Infrared Rule.* If the first absorption band in the infrared spectrum of a hydrogen-bonded molecular crystal is higher for one form than the other, the former may be assumed to have the larger entropy.

The Gibbs free energy difference, ΔG, between two polymorphs, A and B, reflects the ratio of "escaping tendencies" of the two phases. The escaping tendency is termed the fugacity, f, which is proportional to the thermodynamic activity, a, which is itself approximately proportional to the solubility, s, provided that the laws of dilute solution apply (1). Therefore, the decrease in Gibbs free energy, ΔG, as Form B transforms spontaneously to Form A is given by

$$\Delta G(\text{B} \rightarrow \text{A}) = -RT \ln(f_\text{B}/f_\text{A}) = -RT \ln(a_\text{B}/a_\text{A}) \cong -RT \ln(s_\text{B}/s_\text{A})$$

According to the van't Hoff equation, $\ln(s)$ is a linear function of $1/T$. When the solubilities of A and B are determined at different temperatures, two curves, $\ln(s_\text{A})$ vs. $1/T$ and $\ln(s_\text{B})$ vs. $1/T$, can be drawn. The intersection point of the two curves corresponds to the transition temperature of the two forms, A and B. This method has been applied to the polymorphic systems comprising gepirone hydrochloride (7) and 3-amino-1-(*m*-trifluoromethylphenyl)-6-methyl-1H-pyridazin-4-one (8). Similarly, heats of solution can also be applied to estimate the phase transition temperature of a pair

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of polymorphs A and B (6). Then, if the heat capacity difference, ΔC_p, between two polymorphs is negligible, the transition temperature, T_t, is given by:

$$T_t = (\Delta H_A - \Delta H_B)/[(\Delta H_A - \Delta H_B)/T_o - R \ln (J_B/J_A)]$$

where ΔH_A and ΔH_B are the heats of solution, and J_A and J_B are the intrinsic dissolution rates of polymorphs A and B, respectively, at a certain known temperature, T_o (6). If ΔC_p of the polymorphs is known, a more accurate equation is available (6). ΔG at a temperature near the temperature, T_o, may be estimated to yield a plot of ΔG vs. T, from which the transition temperature may be estimated from the intercept of the plot with the T axis (i.e., where $\Delta G = 0$). Therefore, enantiotropy or monotropy can be inferred from T_t after comparison with the melting points of the two polymorphs.

Neotame (*N*-(3,3-dimethylbutyl)-L-α-aspartyl-L-phenylalanine 1-methyl ester) is an alkylated derivative of the dipeptide sweetener, aspartame, and has intense sweetening potency. Discovered by Nofri and Tinti, neotame is currently being developed by the NutraSweet Company (9). Neotame has recently been approved by the U.S. Food and Drug Administration for approval as a general-use sweetener in food and beverages. Neotame exists as several solvates, including neotame monohydrate (10) and neotame methanol solvate (11), and as several polymorphic neotame anhydrates (12–14).

MATERIALS AND METHODS

Materials

Neotame monohydrate with a water content of 4.64% was supplied by the NutraSweet Company (Mount Prospect, IL, USA). 2-Propanol was purchased from Pharmco™ (Brookfield, CT, USA).

Experimental Techniques

Powder X-Ray Diffractometry

Powder X-ray diffraction (PXRD) patterns were determined at room temperature using an X-ray diffractometer (Siemens, model D-5005, Karlsruhe, Germany) with Cu Kα radiation at 40 mA, 45 kV. The scanning conditions are described in the following experimental methods.

Quantitation of the Polymorphic Mixtures of Neotame Anhydrate A and G

Among the seven polymorphs, only A and G were phase-pure. Hence, quantitative PXRD was developed for the analysis of polymorphic mixtures of A and G. For standard curves, mixtures of freshly prepared crystalline powders of Forms A and G (15), containing the following weight percentages of Form A, were prepared: 1, 2, 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 92, 94, 94, 96, 98, and 99%. After weighing these powders, Forms A and G were intimately mixed by a vortex mixer for about 15–20 s.

Forms A and G have distinctive PXRD patterns (Fig. 1), in which the strongest peaks for distinguishing and quantitating the two polymorphs are: 7.1° 2θ for Form A and 7.9° 2θ for Form G. Immediately before X-ray scanning the polymorphic mixtures were gently ground by hand with a pestle in a mortar for 1–2 min to reduce the crystals to approxi-
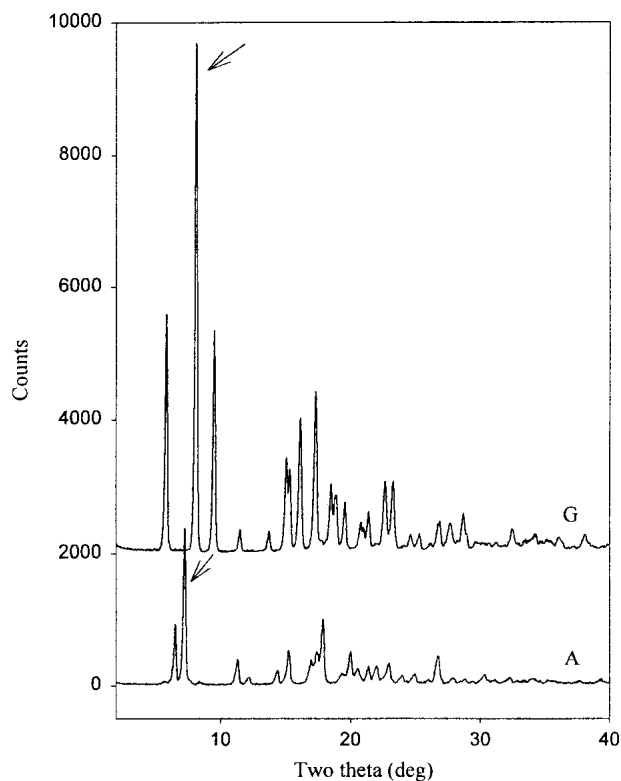

Fig. 1. Powder X-ray diffraction patterns of Forms A and G.

mately spherical particles to prevent preferred orientation. Each polymorphic mixture in the powder X-ray diffractometer (Siemens D5005) was scanned from 6.5 to 8.5° 2θ by a Cu-Kα radiation source. The step size was 0.01° and the residence time was 1.0 s. The peak height and peak area of each of the two peaks, 7.1° 2θ for Form A and 7.9° 2θ for Form G, were measured by means of the instrumental software. The standard curves were drawn based on peak height, P, and peak area, Q. $P_A/(P_A + P_G)$ and $Q_A/(Q_A + Q_G)$ were each plotted against the weight percentage of A, where P_A and P_G are the peak heights and Q_A and Q_G are the peak areas of the respective peaks.

Solid-State Stability of Neotame Anhydrate Polymorphs

The solid-state stability of four neotame anhydrate polymorphs A, D, F, and G were studied by PXRD. Six 50:50 binary mixtures of the four polymorphs were placed under 0%RH and at 23 and 70°C, respectively. The change of the composition of each mixture was monitored periodically by PXRD. The scanning conditions were 6.5–8.5° 2θ, 0.01° step size and 1 s residence time for mixtures of A and G. However, for other polymorphic mixtures, the conditions were 2–10°, 0.05° step size, and 1 s residence time.

Solution Calorimetry

An isoperibol solution calorimeter (model 4285, Calorimetry Sciences Corp., Pleasant Grove, UT, USA) was used to determine the enthalpy of solution of neotame anhydrate polymorphs (50 mg samples) in 2-propanol (25.0 ml) at 25°C. The calorimeter was calibrated with a programmed heater attached to the instrument before each measurement.

Determinations of the Intrinsic Dissolution Rates of A and G

A dissolution apparatus, designed to maintain constant hydrodynamic conditions was employed to determine the intrinsic dissolution rate of compacted disks of A or G (16,17). The dissolution cell consisted of a poly(methyl methacrylate) beaker, a top cover with an outlet for sampling, and a stainless steel sample holder for the compact. Samples (about 300 mg) were compressed at 5000 lb (2250 kg, 2.81×10^2 MPa) for 1 min under a hydraulic press (Carver Laboratory Press, model C, Menomonee, WI, USA) to form the compact (diameter 1 cm, area 0.785 cm^2). The sample holder was then screwed into the dissolution beaker, and 500 ml of 2-propanol, pre-equilibrated at the experimental temperature, was poured into the dissolution beaker. At a fixed height above the sample, a stirrer was rotated at 50 rpm to provide constant hydrodynamic conditions. Sink conditions were maintained during the course of dissolution. Samples were taken every 5 min for 30 min and were analyzed at 258 nm by a calibrated ultraviolet spectrometer (Beckman DU 7400, Irvine, CA, USA).

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) employed a differential scanning calorimeter (Dupont, model 910, TA Instruments, New Castle, DE, USA) equipped with a data station (Thermal Analyst 2000, TA Instruments, New Castle, DE, USA) and calibrated with indium. All DSC runs were performed in crimped pans under a nitrogen purge at 50 ml/min and at a heating rate of 10°C/min.

RESULTS AND DISCUSSION

Among the polymorphs of neotame anhydrate, only Forms A, D, F, and G are available in bulk, as stated previously (15). Therefore, these four forms were characterized in detail, and their quantitation by PXRD and their thermodynamic and kinetic stability are described in this paper. Because the crystals were reduced to approximately spherical particles by gentle grinding immediately before scanning, preferred orientation was effectively prevented.

Figure 2 shows two standard curves based on peak height and peak area. Both curves show good linearity, as indicated by R^2, and are almost superimposable: $y = 0.002380 + 1.015x$, $R^2 = 0.9984$ (peak area); $y = 0.000645 + 1.0035x$, $R^2 = 0.9988$ (peak height). The polymorphic mixture containing 1%(w/w) Form A clearly shows the characteristic peak of A at 7.1° 2θ, suggesting that the detection limit of Form A in the polymorphic mixture is below 1%(w/w). However, the characteristic peak of G at 7.9° 2θ cannot be detected for the polymorphic mixture containing 1%Form G. The detection limit of Form G in the mixture therefore exceeds 1%(w/w), probably between 1–2%(w/w), so the point within this range was not included in the linear regression. The above results show that PXRD is a simple and accurate method to assay polymorphic mixtures of Forms A and G. As expected, polynomial functions with four parameters provided improved fits to each of the two standard curves, thus:

$$y = 1.6067 + 0.67064x + 9.2003 \times 10^{-3}x^2 - 6.1517 \\ \times 10^{-5}x^3, R^2 = 0.9993 \text{ (peak area)};$$

$$y = 1.4957 + 0.72018x + 7.4334 \times 10^{-3}x^2 - 4.9143 \\ \times 10^{-5}x^3, R^2 = 0.9993 \text{ (peak height)}.$$
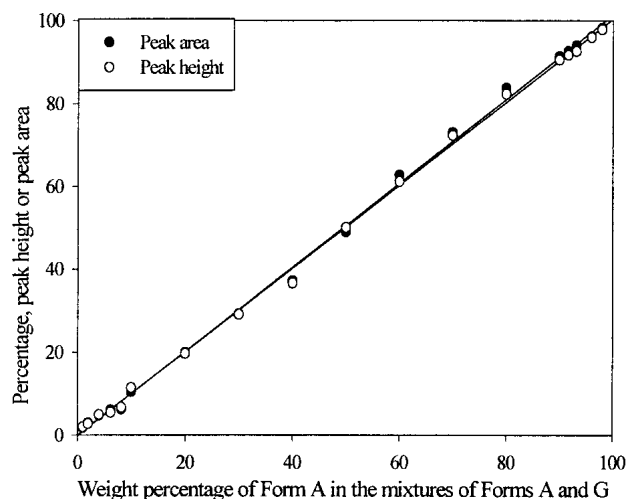

Fig. 2. Standard plots for the quantitative analysis of polymorphic mixtures of Forms A and G based on peak area (●) and peak height (○), using powder X-ray diffractometry at 7.1° 2θ for Form A and 7.9° 2θ for Form G.

Comparison of the coefficients of determination, R^2, for the respective two-parameter (linear) and four-parameter equations, suggests little advantage in the four-parameter equation. Therefore, for simplicity and convenience, the linear equations are preferred.

As described in a previous work (15), the rank order of the densities of the neotame anhydrate polymorphs at 23°C is F > D > A > G. Therefore, if we assume that the rank order of the densities of the polymorphs does not change with temperature, corresponding to equal thermal expansivities, the density rule (2) suggests that the relative stability of these four polymorphs at 0 K is F > D > A > G.

Using solution calorimetry, the enthalpies of solution of Forms A, D, F, and G were determined at 25°C in 2-propanol. 2-Propanol was employed instead of water, because water causes hydration transitions of the anhydrates to form the monohydrate and because 2-propanol is the better solvent for neotame. The endothermic enthalpy of solution follows the rank order: G (29.71 ± 0.82 kJ/mol, n = 4) > A (28.48 ± 0.51 kJ/mol, n = 4) > D (20.43 ± 0.45 kJ/mol, n = 4) > F (18.77 ± 0.31 kJ/mol, n = 4). This rank order also applies to the endothermic lattice enthalpy. The first law of thermodynamics implies that the choice of solvent does not affect the enthalpy differences between the polymorphs, nor the rank order observed.

By conventional DSC, the melting points and heats of fusion are 92°C and 24.7 kJ/mol for Form A; 94°C and 15.3 kJ/mol for Form D; 92°C and 11.1 kJ/mol for Form F; 112°C and 18.5 kJ/mol for Form G. The melting points of the four polymorphs follows the rank order, G > D > A ≈ F, whereas the rank order for the heats of fusion is A > G > D > F. According to the heat of fusion rule (2), the polymorphic pairs, A-D and A-G, are enantiotropic. On the other hand, the three polymorphic pairs, D-F, D-G, and F-G, are monotropic. However, because Forms A and F have closely similar melting points, their thermodynamic relationship requires further clarification.

The intrinsic dissolution rates, J, of Forms A and G in 2-propanol at 25 to 32°C were determined as described. The

linear van't Hoff plot of ln(J) against $1/T$ was drawn for each Form, A and G (Fig. 3). When extrapolated, the two lines intersect at about 55°C, corresponding to an estimated phase transition temperature, T_t, suggesting enantiotropy of Forms A and G, with A thermodynamically stable below this temperature and G thermodynamically stable above this temperature. Because the van't Hoff plot assumes negligible difference in heat capacity between the dissolved solute and solid solute, constancy of activity coefficient of the dissolved solute, and negligible experimental errors, the extrapolations will not be truly linear nor reliable. Consequently, this extrapolated value provides only a rough estimate of T_t for A ⇔ G. However, intersection of the two plots appears likely, suggesting that Forms A and G are members of an enantiotropic pair, agreeing with the deductions from the melting data. The 95% confidence intervals of the two curves show that the possible minimum value of T_t is 35°C, whereas the possible maximum value of T_t is an indeterminate high temperature, leaving open the possibility of a monotropic system. However, T_t, calculated from Eq. (2), is −92°C, a much lower value. This discrepancy may arise from the following possible errors: (a) omission of the C_p terms from Eq. (2); (b) experimental error in the measured intrinsic dissolution rates and heats of solution.

The solid-state stability of 50:50 binary polymorphic mixtures of neotame anhydrate polymorphs was studied by PXRD. At 23°C and 0%RH, the polymorphic mixture, A + G, shows no change in the fraction of A (F_A) within 4 months, indicating that the phase transition from G to A is relatively slow. Under the same conditions, the polymorphic mixtures, A + D, A + F, D + F, D + G, and F + G show no change in peak intensity within 5 months. The slow kinetics of phase transition at room temperature (23°C) among the polymorphs indicates appreciable solid-state stability.

However, at 70°C and 0%RH, Form A converts to Form G rather quickly. Figure 4a shows an exponential-like decrease of F_A with respect to time, t, in days, for A + G mix-

Fig. 4. Phase transition time profile from A to G at 70°C and 0%RH. (a) Plot of fraction of A, F_A, against time. (b) Plot of $\log_{10}F_A$ against time.

tures. The logarithmic plot (Fig. 4b) clearly shows two straight lines, which intersect at $t = 42$ days, corresponding to different kinetics of phase transition before and after this time point. The two equations for the two lines are: $\log(F_A) = -0.6829 - 0.0279 \times t$ ($R^2 = 0.9993$, before Day 42) and $\log(F_A) = -0.1376 - 0.0419 \times t$ ($R^2 = 0.9901$, after Day 42). The change in slope may arise from a change of mechanism of the phase transition, i.e., crystal growth of Form G at the expense of Form A, in different F_A ranges. When $t > 42$ days, F_A is < 15.6% and the transformation rate is faster (Fig. 4b). The transformation of Form A to Form G at 70°C indicates that the phase transition temperature between A and G lies below 70°C. However, the lower limit of the transition temperature is 35°C from the van't Hoff plot (Fig. 3). Therefore, Forms A and G constitute an enantiotropic pair.

At 70°C and 0%RH, the polymorphic mixture of A and D (Fig. 5a) shows no interconversion within 30 days. However, at Day 30 the color of the mixture changes from white to pale yellow. At Day 47 the yellow mixture begins to form a glass-like phase for which the PXRD peak intensities have decreased dramatically. At Day 61 the sample has formed a
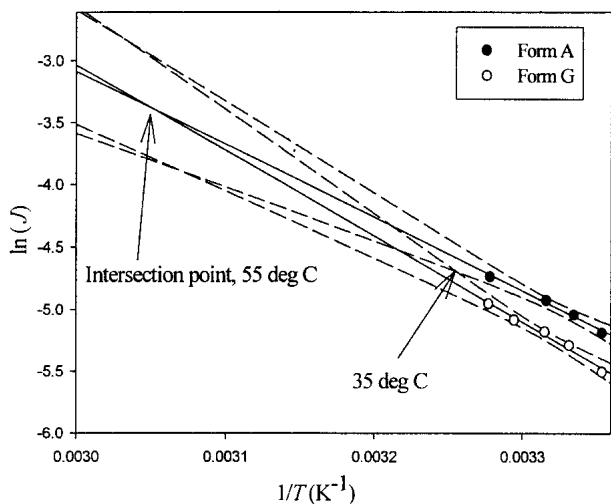

Fig. 3. Van't Hoff plots of the natural logarithm of the intrinsic dissolution rates, J, of Forms A (●) and G (○) in 2-propanol against the reciprocal of the absolute temperature, T. The broken lines indicate the limits of the 95% confidence intervals of the linear regression lines.
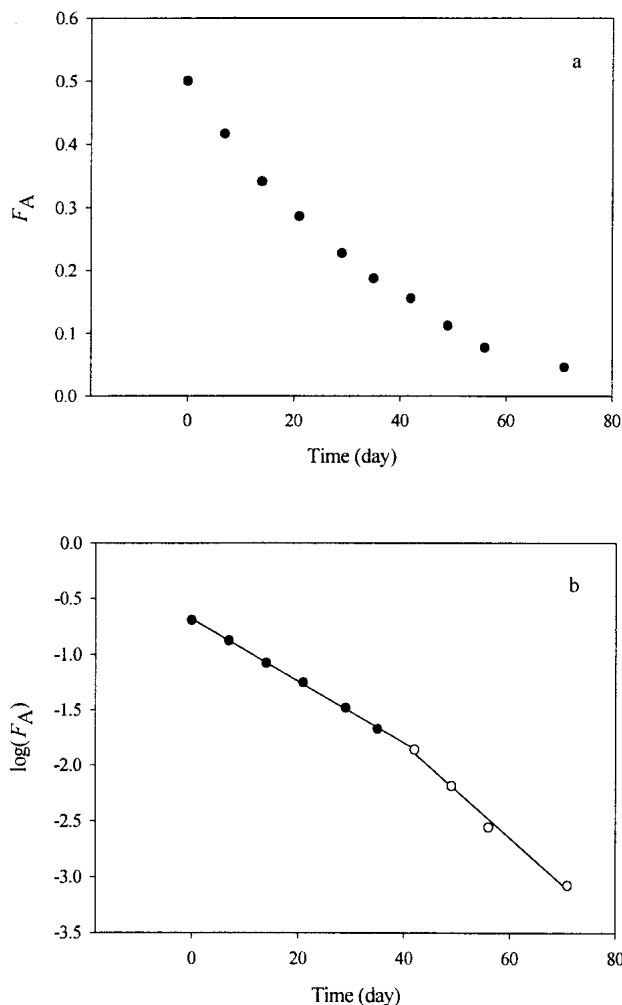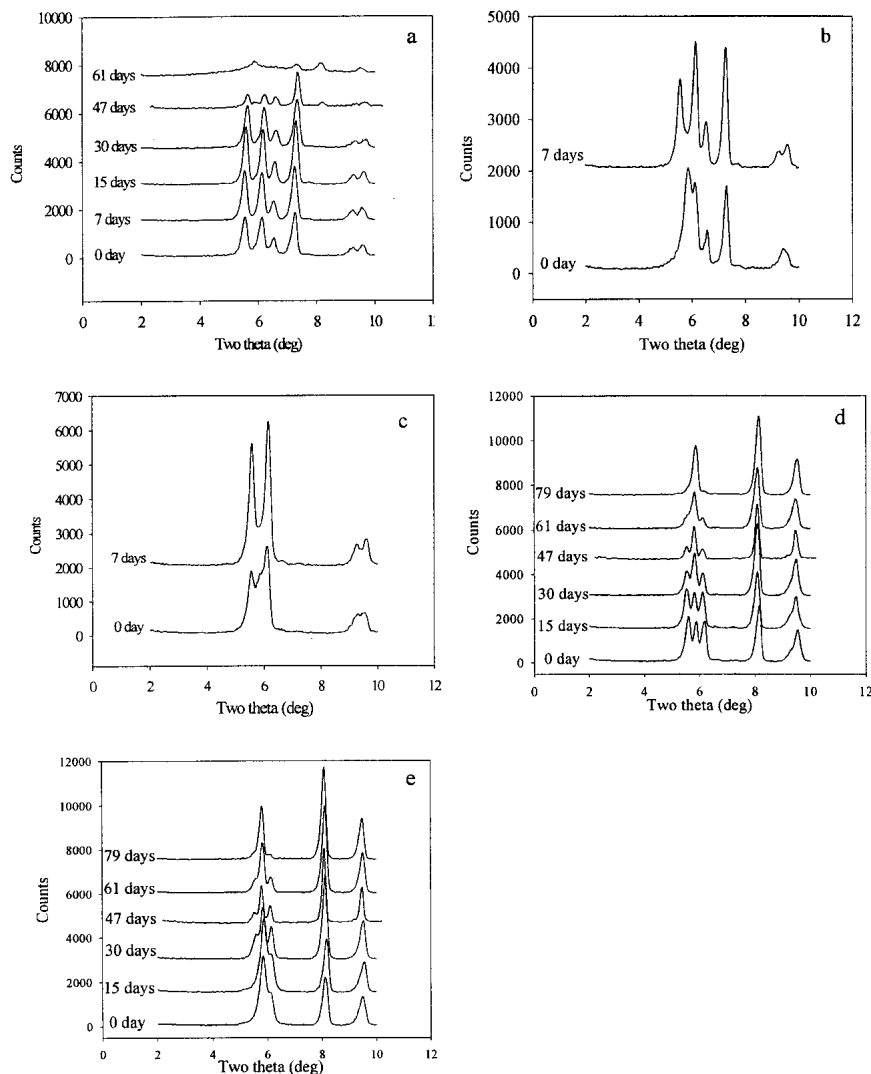
Fig. 5. Powder X-ray diffraction patterns showing the phase transitions of binary polymorphic mixtures at 70°C and 0%RH: (a) A + D, (b) A + F, (c) D + F, (d) D + G, and (e) F + G.

glass-like melt and the characteristic peaks of Form G have begun to appear. The color change indicates chemical decomposition of neotame at 70°C, which then leads to melting of the sample and the formation of a glass-like phase with a low crystallinity. Subsequently, the more stable Form G crystallizes out. In the polymorphic mixtures of A and F (Fig. 5b), and D and F (Fig. 5c), Form F initially converts to Form D. Afterwards the A + F mixture behaves like the A + D mixture. This phenomenon also suggests that Form F is thermodynamically less stable than Form D at 70°C.

At 70°C and 0%RH, the polymorphic mixture D + G (Fig. 5d) shows little change within 15 days. From Day 15 to Day 61 the PXRD peak intensities of Form D decrease, and the color of the sample becomes pale yellow at Day 61. At Day 79 the mixture has transformed to Form G, as indicated by the total disappearance of Form D PXRD peaks. Consequently, at 70°C Form G is more stable than Form D. In the F + G mixture (Fig. 5e), Form F converts to Form D within seven days, similar to the A + F mixture. Afterwards the F + G mixture shows the same phenomena as the D + G mixture. Overall, the solid-state stability of Forms A, D, F, and G at

70°C follows the rank order: G > D > F and G > A. The relatively stability of members of the polymorphic pairs, A-D, A-F, could not be determined at 70°C.

Among the four thermodynamic rules, the heat of transition rule and the heat of fusion rule have rare exceptions, whereas the density rule and the infrared rule have significant exceptions (2–4). Hence, the conclusion drawn from the density rule can be considered as a rough guide, whereas the heat of fusion rule is a more reliable tool in the determination of the thermodynamic relationships among these polymorphs. Based on the heat of fusion rule, the intrinsic dissolution rates of Forms A and G, and the relative solid-state stability studies at 70°, Fig. 6 provides an approximate free energy diagram for the four anhydrate polymorphs. In this plot, parts of the free energy curves of Forms A and F are dashed lines, indicating that their thermodynamic relationship is yet to be determined.

CONCLUSIONS

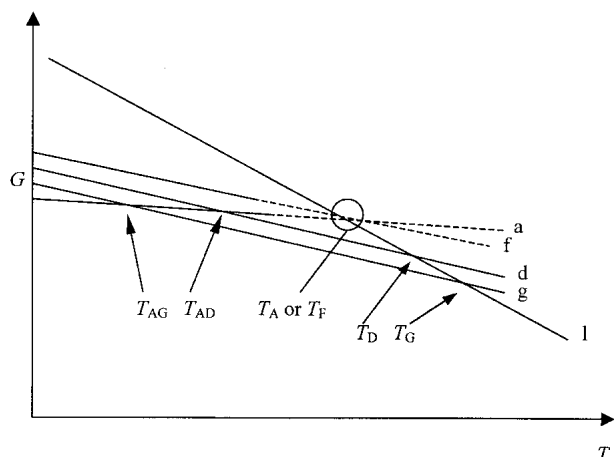PXRD provides a convenient method for the quantitative analysis of polymorphic mixtures of Forms A and G. This

Fig. 6. Schematic free energy (*G*) vs. temperature (*T*) diagram of Forms A, D, F, and G, where a, d, f, g, l are the free energy curves for Forms A, D, F, G, and liquid neotame, respectively. T_{AG} is the phase transition temperature of Forms A and G, T_{AD} is the phase transition temperature of Forms A and D, whereas T_A, T_D, T_F, and T_G are the melting points of the four polymorphs A, D, F and G, respectively.

method provides detection limits of <1%(w/w) for A in G or 1–2%(w/w) for G in A for and the standard curves are quite linear.

Polymorphic pairs A-G, A-D are enantiotropic, whereas D-G, D-F, and F-G are monotropic. The thermodynamic relationship between A and F is still unknown. At 70°C the solid-state stability follows the rank order: G > D > F and G > A. The relative stability of A-D or A-F has not been determined. The phase transition temperature between Forms A and G are estimated to lie within 35–70°C. At 23°C the rate of transition among the four polymorphs is not detectable over several months. However, at 70°C, the transformation proceeds relatively quickly.

ACKNOWLEDGMENTS

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