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Thermal Behavior of a Pharmaceutical Solid Acetaminophen Doped with *p*-Aminophenol

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ABSTRACT Thermal behavior of a series of acetaminophen (APAP) doped with *p*-aminophenol (PANP) was studied by differential scanning calorimetry (DSC) to determine whether it exhibited a eutectic system. Within the temperature range of 120 to 200° C, accurately weighed (1-2 mg) samples sealed in hermetic pans were calorimetrically scanned with a low scanning rate of 1° C/min. The mixture formed a single eutectic with the composition ratio APAP/PANP of 0.6/0.4 at a temperature of 138° C, where it liquefied. Melting began as early as at the eutectic point, which was below the melting temperature of APAP (169° C). The melting point as well as heat of APAP fusion was depressed with the increase in doped PANP. It was postulated that there might be a deficit heat of APAP fusion in APAP doped with PANP, which was coincident with the heat consumed by early liquefaction. The deficit heat was used to correct fraction molten in the van't Hoff law of purity determination. It was found that the purity determination of APAP doped with PANP was comparable to the UV-spectroscopic method up to the maximum doped PANP level of 8 mol percent. It was concluded that DSC was able to approach early heat of liquefaction of APAP doped with PANP. The van't Hoff law may be applicable to the determination of APAP with the presence of PANP as a eutectic impurity.

Key Words: DSC, Thermal Behavior, the van't Hoff Law, Purity Determination, Acetaminophen, *p*-Aminophenol, Eutectic

INTRODUCTION

Acetaminophen (APAP), a safe and effective analgesic and antipyretic, has been available on the worldwide market for a long period of time. Given this mass distribution, it has been preferable to have the simplest, least expensive, and fastest methods of tablet preparation s(ie, utilizing direct compression). The direct compressible APAP crystalline has been demonstrated [1-2]. Besides the active drug, only minimal amounts of other substances may be present in the APAP crystalline product. One of those that may be critical to the quality of APAP is its degraded product, *p*-aminophenol (PANP). The USP monograph indicates a limited assay of PANP as one APAP impurity specification [3]. The assay was based on the spectroscopic method that requires prior sample preparation.

Differential scanning calorimetry (DSC) may be a simple and rapid method of estimating the purity of materials [4]. It may also be applicable to many pharmaceuticals including APAP [5]. The method is based on the van't Hoff law of melting point depression expressed as:

$$T_0 - T_m = \frac{R T_0^2 X_2}{\Delta H_f} \bullet \frac{1}{F} \qquad (1)$$

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Where, T_0 and T_m are absolute temperatures of fusion of pure and impure materials, DH_f is the molar enthalpy of fusion, F is the fraction molten corresponding to T_m, and R is the gas constant. A plot of T_m against $1/F$ should yield a straight line having a slope and intercept of $\frac{RT_0^2X_2}{\Delta H_f}$ and T_0, respectively. The mole fraction of impurity (X_2) is then obtained from the slope of the plot [4].

In practice, the plot between T_m and $1/F$ was not linear [4-5]. Liquefaction began at the eutectic point that may be far below the range of melting temperature of the material being examined [6]. With a minute amount of eutectic impurities, the magnitude of the early heat of liquefaction was difficult or impossible to measure. Several methods of heat correction have been suggested to linearize the van't Hoff plot [4]. The most frequently applied methods were based on graphical calculation and fitting so that the heat was not directly determined [4]. The purpose of this study was to determine if PANP behaves as a eutectic impurity in the early heat of liquefaction of APAP doped with PANP. In addition, based on the early heat of liquefaction, van't Hoff plot linearization compared the amount of APAP determined from equation (1) to that from the spectroscopic method.

MATERIALS AND METHODS

Analytical grade APAP (A-5000, Sigma Chemical Co., St. Louis, MO) and PANP (MERCK-Schuchardt, Darmstadt, Germany), reference standard having purity level more than 99 per cent label amount, were employed as a model of the binary mixture under study. Nighty-five percent vol/vol ethanol was used as a solvent for mixture preparation.

Preparation of Mixtures

A series of APAP-PANP binary mixtures with APAP mole fractions (X_1) of 0.97, 0.95, 0.92, 0.90, 0.80, 0.60, 0.20, and 0.05 was prepared as follows. The pre-determined quantities of APAP and PANP were accurately weighed (5-digit analytical balance, I-1700, Sartorius, Goettingen, Germany) and dissolved in 95% vol/vol ethanol. The solvent was then rapidly evaporated under the controlled temperature of 70+2° C, allowing APAP as well as PANP to recrystallize. The obtained white solid powders were desiccated overnight for sorbed moisture removal prior to use.

The mixtures were subjected to UV-spectroscopy (Spectronic Genesys-5, Milton Roy, Rochester, NY.) to quantitatively determine absorbance. Prior to the determination, a solution of 10 µg/mL APAP in 95% vol/vol ethanol was spectroscopically scanned at wavelengths of between 200 and 400 nm; maximum absorption was illustrated at 250 nm. A series of alcoholic solutions of APAP concentrations between 2 and 7 µg/mL was then spectroscopically measured at a 250-nm wavelength to construct a calibration curve yielding a linear line with a correlation coefficient of 0.9997. For each of the mixtures, a 0.01-g sample was accurately weighed and volumetrically dissolved in 2.5 L of 95% vol/vol ethanol. The 250-nm wavelength UV-absorbency was measured using 95% vol/vol ethanol as a blank. In addition to fixed wavelength measurement, UV-spectroscopic scanning was also done on PANP and the binary solid mixtures in the identical manner as the APAP scanning. Some of the scanning profiles are shown in **Figure 1.**

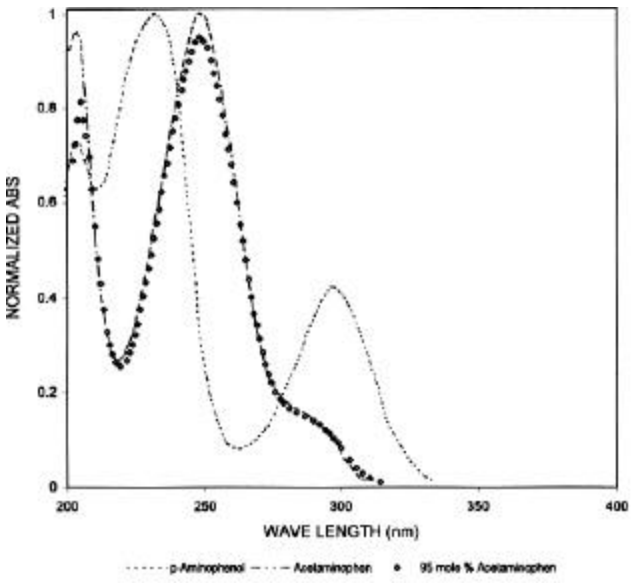

Figure 1. Spectroscopic scanning profiles of APAP, PANP, and APAP doped with PANP at 0.05 mole fraction.

PANP exhibited some absorbency at the UV wavelength of APAP maximum absorption. It was shown that the UV absorption of PANP alcoholic solution was possible, although it was suggested in the USP monograph that free PANP exhibited maximum absorption at a visible wavelength [3]. With the aid of in-house software, numerical separation and fitting were used to rid UV absorbency of PANP from the 250-nm wavelength absorbency of alcoholic solutions of the binary mixtures prior to APAP concentration determination by the calibration curve described above.

Differential Scanning Calorimetric Studies on Acetaminophen-p-Aminophenol Solid Mixtures

The endotherms of APAP-PANP solid mixtures were obtained using a model DSC-7 differential scanning calorimeter (Perkin Elmer, Norwalk, CT). A very small amount of sample and a low scanning speed were used so that equilibrium transition was approached as closely as the kinetic process allowed [7]. For each of the solid mixtures, 3 specimens of accurately weighed (1-2 mg) sample were placed in DSC pans. The samples were hermetically sealed and equilibrated at 50° C for 1 minute. They were individually run against an empty pan using 2 steps of heating rates ie, a rate of 15° C/min followed by that of 1° C/min, covering the temperature range of 50 to 120° C and 120 to 200° C, respectively. Individual APAP and PANP were also subjected to calorimetric scanning using the same method.

Since there was no trace of transition during the 50 to 120° C temperature range, the DSC information of the range was discarded. For each of the DSC scanning profiles of the 120 to 200° C temperature range, heat of fusion of major component and eutectic heat of liquefaction were determined (Pyris software, Perkin Elmer). Eutectic composition was analyzed by plotting the mole fraction of APAP component (X_1) against the corresponding eutectic heat of liquefaction. A phase diagram of binary mixtures (ie, melting point depression- X_1 profile), was then constructed.

Some of the endotherms of APAP in mixtures having X_1 of approximately 0.90, 0.92, 0.95, and 0.97 were studied to determine the compositions of their components according to equation (1). The first 5% to 30% portion of each of APAP endothermic fusion peak was used for calculating fraction molten (F). F-values were then corrected based on the postulated early heat of liquefaction. Its reciprocal was plotted against the corresponding absolute temperature. The mole fractions of APAP were determined and compared with those determined by the UV-spectroscopic method.

RESULTS AND DISCUSSION

DSC Endotherms of Acetaminophen, p-Aminophenol, and Their Mixtures

In the study, 1-2- mg accurately weighed samples were run at a scanning speed of 1° C, which was essentially as low as that suggested in the literature (<5° C/min) [8]. The endotherms of APAP and PANP are showed in **Figure 2.**

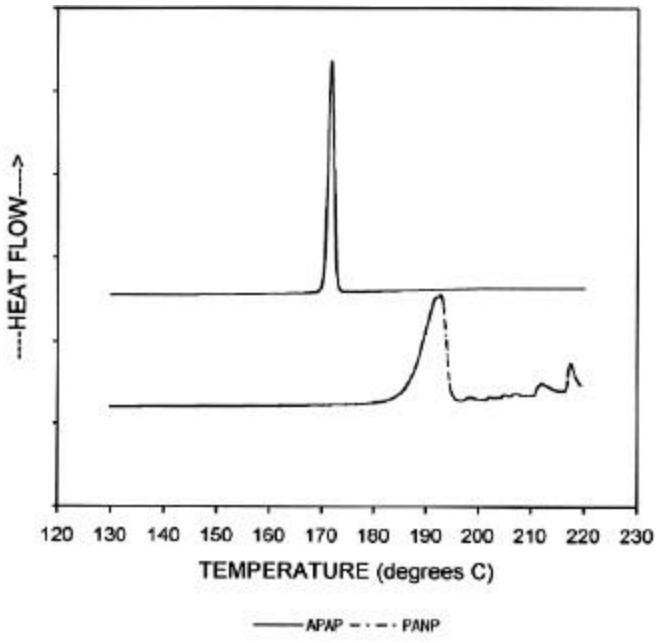

Figure 2. Endotherms of APAP and PANP showing melting transitions at 169 and 190°C, respectively.

Some of the endotherms of mixtures at X_1 levels of 0.97, 0.95, and 0.90 are illustrated in **Figure 3.**

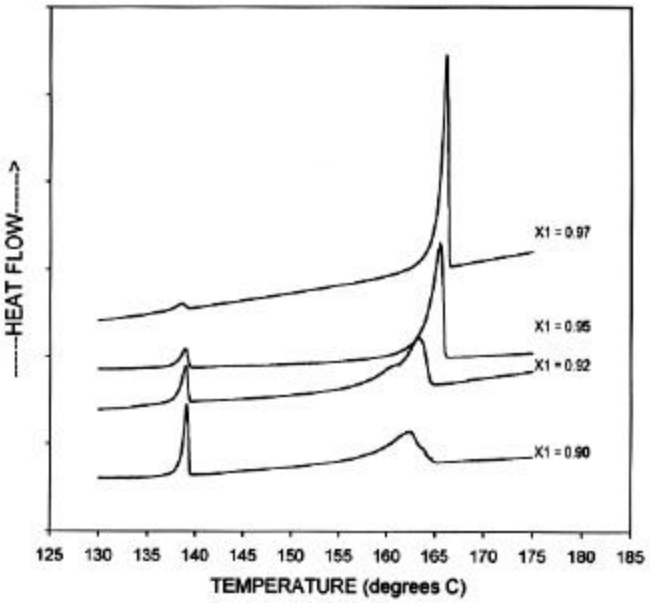

Figure 3. Endotherms of APAP doped with PANP at various mole-fraction levels of APAP (X_1) showing increased eutectic endotherm at 138° C.

Their characteristic melting is also tabulated in **Table 1**.

Table 1. Characteristic Endothermic Peaks Found in Thermograms of APAP, PANP, and Their Mixtures

Endotherm	Onset in ° C	Peak in ° C	DH_f†
APAP*	168.58 (1.54)	169.00 (1.50)	26.030 (1.154)
PANP*	186.27 (0.38)	190.31 (3.18)	29.263 (1.532)
Mixtures			
0.90 X_1	156.67 (3.24)	162.48 (0.11)	17.085 (2.067)
0.92 X_1	161.54 (0.23)	163.32 (0.05)	19.120 (0.700)
0.95 X_1	136.85 (0.97)	165.16 (0.36)	19.791 (1.848)
0.97 X_1	165.08 (0.03)	166.91 (1.01)	22.610 (0.195)
Eutectic‡	136.82 (2.02)	138.20 (1.42)	-§

*Values are mean (standard deviation) calculated from 3 replications.

†Molar heat of fusion in kilo-joules/mole.

‡Values are mean (standard deviation) calculated from 10 different mole fractions of APAP-PANP mixtures.

§Heat of eutectic melt increased with the increase in mole fraction of minor component (PANP).

As seen in **Figures 2** and **3** and **Table 1**, there was a sharp endothermic peak at 169° C. It has been reported that APAP crystallized in a hydroalcoholic solution yielded monoclinic form [1] and melted at a temperature of 169° C [2]. It is concluded that the APAP crystalline used as well as the recrystallized ones in the mixtures may exhibit a monoclinic form, and no polymorphs of APAP were presented.

Eutectic Melt and Phase Diagram of Acetaminophen-p-Aminophenol Mixtures

As seen in **Figure 3**, 2 endothermic peaks occurred. One with major heat of fusion appeared at a high temperature level corresponding to APAP melting as previously discussed. The other occurred at 138° C. Apparently, the peak position did not vary with the level of component (**Table 1**), whereas the magnitude of heat increased with the increase in PANP mole fraction. It was observed that the mixtures liquefied at the temperature that was the eutectic point. A plot of the eutectic peak area in joules/g (DH_{eu}) against X_1 is illustrated in **Figure 4**.

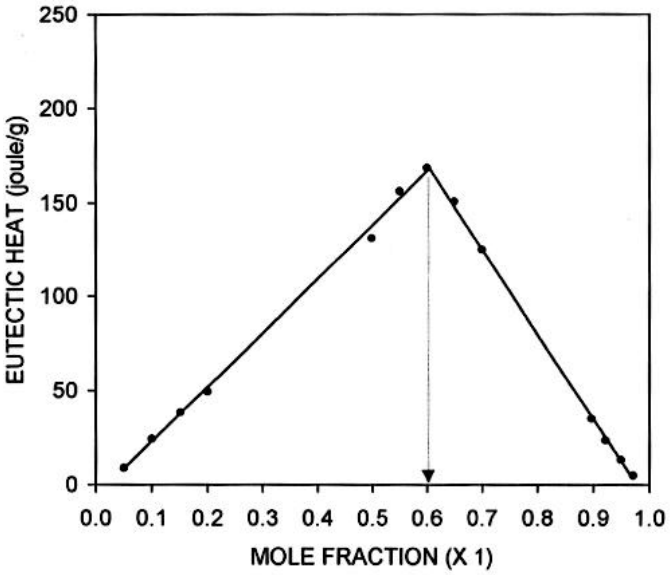

Figure 4. The plot of eutectic heat in joules per gram against APAP mole fraction (X_1).

As seen in the figure, 2 curves corresponded to X_1 as a solvent and a solute, respectively. These 2 curves showed an identical coordinate

(ie, the intersection of the curve) at the composition of eutectic [7]. The information from **Figure 4** indicated

that the eutectic mixture contained APAP and PANP at a mole ratio (X_1/X_2) of 0.6/0.4.

The information on temperatures of fusion allowed construction of the simple phase diagram of APAP-PANP mixture shown in **Figure 5**.

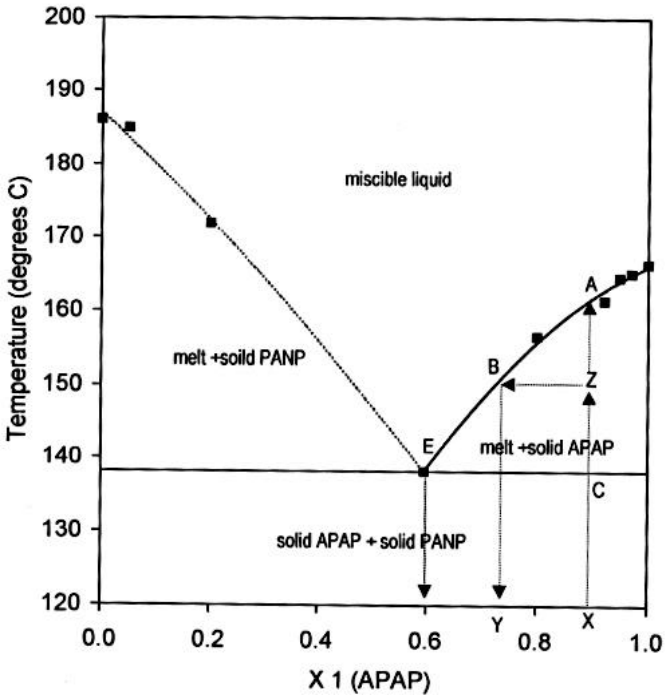

Figure 5. Phase diagram of APAP-PANP mixture with a single eutectic point.

The figure shows two melting-point-depression curves of APAP and PANP, starting with their melting points reduced to the same minimum coordinate (X_1 of 0.6, temperature of 138° C) that was a eutectic. A horizontal line drawn through the eutectic illustrates the boundary between physical mixtures of solids and mixtures of melt and individual solids. Upon heating, a eutectic liquid phase presented at 138° C, followed by melting of the remaining solids along the melting-point-depression curves. A trace amount of PANP may dissolve in APAP melt and a system may approach ideal solution [6]. Theoretically, then, it is possible for the van't Hoff law to determine APAP composition in the mixtures.

The Determination of Acetaminophen Composition by the van't Hoff Law

In theory, a melting transition of an absolute pure crystalline should occur within anarrow range whereas an impurity, when presented, could broaden the melting range [4, 8]. It was observed that an APAP endotherm became broader when it was doped with PANP (ie, the more PANP presented, the broader the peak) (**Figure 3**).

Although the van't Hoff law assumed that the molar enthalpy of fusion of the main component was constant over temperature range and independent of the nature and amount of impurity [4], the heat of APAP fusion decreased with increase in PANP mole fraction (**Table 1**). If the assumption of a constant molar enthalpy of fusion holds, it is then hypothesized that a deficit heat function may occur coincidentally with the early melt previously suggested. Taken as a thermodynamic function of state, the deficit heat function denoted as DH_d should be equal to the difference between molar enthalpy of fusion of APAP and that in mixture, expressed as

$$\Delta H_d = \Delta H_f - \Delta H_f^i \qquad (2)$$

where, ΔH_f^i is the molar heat of APAP fusion where PANP presented. This difference in molar heat was then used to correct the fraction molten (f):

$$F = \frac{A + \Delta H_d}{\Delta H_f^i + \Delta H_d} \qquad (3)$$

where, A is the partial area of APAP endotherm at corresponding temperature T_m.

Figure 6 shows the van't Hoff plots both before and after fraction molten correction; after correction the curve becomes linear. The van't Hoff plots after correction of APAP fusion at X_2 levels of 0.03, 0.05, 0.08, and 0.10 are illustrated in **Figure 7**. The values of X_1 determined by the van't Hoff plot and the corresponding values determined by UV-spectroscopic method are tabulated in **Table 2**.

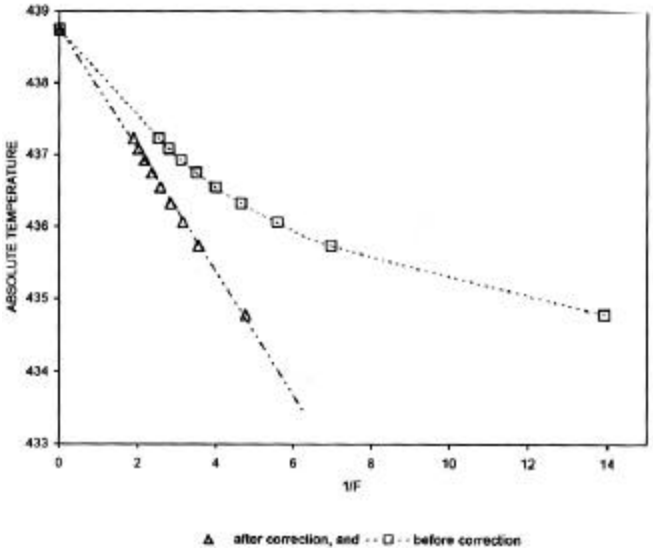

Figure 6. The van't Hoff plots compared between before and after correction by the proposed deficit heat.

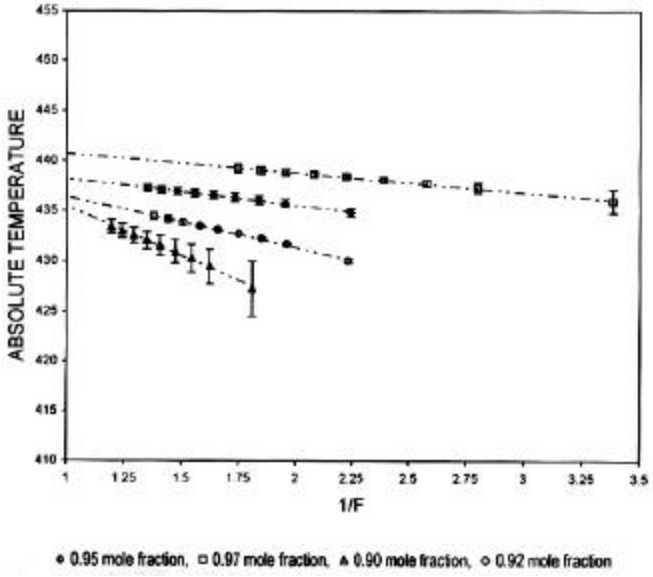

Figure 7. The van't Hoff plots of APAP doped with PANP at various mole fraction levels of APAP (X_1).

It was found that X_1 obtained from the van't Hoff plot at a low level of X_2 agreed with that determined by the UV-spectroscopic method. The value from the van't Hoff plot became deviated significantly from the value determined by UV-spectroscopic method when a high level of X_1 presents, eg, at 0.90 X_1 level, the deviation is as high as –6.17% (**Table 2**).

Table 2. Mole Fractions of APAP (X_1) in APAP-PANP Mixtures Determined from the van't Hoff Plot Compared with Those by UV-Spectroscopic Method*

Expected X_2	X_1^{UV}: UV-spectro-Method	X_1^{DSC}: the van't Hoff plot	Difference (D)†	Deviation %‡
0.10	0.8884 (0.0042)	0.8336 (0.0014)	-0.0548 (0.0044)	-6.17
0.08	0.9094 (0.0069)	0.9135 (0.0018)	+0.0041 (0.0071)	+0.45
0.05	0.9540 (0.0009)	0.9537 (0.0006)	-0.0003 (0.0011)	-0.03
0.03	0.9635 (0.0177)	0.9659 (0.0010)	+0.0024 (0.0177)	+0.25

*Values are mean (standard deviation) calculated from 3 replications.

†$D = X_1^{DSC} - X_1^{UV}$

‡Deviation = $\frac{D}{X_1^{UV}} \cdot 100$

The DSC method of purity determination may be limited to high-purity samples. Previously many investigators estimated different maximum concentration levels for van't Hoff law applicability [4, 8, 9]. Whereas the estimated level was 1 to 5 mole percent [4, 6, 8, 9], this study observed that, with a direct approach to early heat of liquefaction, the level could be as high as 8 mole percent. van-Dooren and Muller [4] have suggested a number of important conditions in the experimental setting of DSC purity determination, most of which were satisfied in this study. These conditions may make it difficult to use the DSC method as an official method of purity determination of pharmaceuticals [10].

CONCLUSIONS

DSC illustrated that an APAP-PANP mixture could form a single eutectic having an APAP/PANP composition ratio of 0.6/0.4 at a temperature of 138° C. A simple phase diagram may describe phase transition

behavior of the mixture. An ideal solution may be approached in the melt of APAP doped with a minute amount of PANP. It was postulated that there might be a deficit heat of APAP equilibrium melt, which coincides with the heat consumed in early eutectic liquefaction. The deficit heat was utilized to correct fraction molten so that the van't Hoff plot was linear. Finally, the purity of APAP that has PANP as an impurity may be satisfactorily determined by the van't Hoff equation for PANP level up to 8 mole percent. Whereas the applicability level was high compared with previous work, the study was limited to a known impurity since the eutectic needed to be determined.

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