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Sublimation Characterization and Vapor Pressure Estimation of an HIV Nonnucleoside Reverse Transcriptase Inhibitor Using Thermogravimetric Analysis

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ABSTRACT

The purpose of this research is to investigate the sublimation process of DPC 963, a second-generation nonnucleoside reverse transcriptase inhibitor for HIV-1 retrovirus, and to better understand the effect of sublimation during active pharmaceutical ingredient (API) manufacture and formulation development, especially the drying processes. Sublimation of DPC 963 at 150°C and above was determined by thermogravimetric analysis-Fourier transform infrared (TGA-FTIR). The rates of sublimation at different temperatures were measured using isothermal TGA. Condensed material was collected and analyzed by differential scanning calorimetry (DSC), x-ray powder diffraction (XRPD), and infrared (IR) spectrometry. Benzoic acid was used as a reference standard to derive a linear logarithmic relationship between sublimation/evaporation rate and vapor pressure specific to the TGA system used in this study. Sublimation and evaporation of DPC 963 were found to follow apparent zero-order kinetics. Using the Eyring equation, the enthalpy and entropy of the sublimation and evaporation processes were obtained. The enthalpies of sublimation and evaporation were found to be 29 and 22 kcal/mol, respectively. The condensed material from the vapor phase was found to exist in 2 physical forms, amorphous and crystalline. Using benzoic acid as a reference standard, vapor pressure of DPC 963 at different temperatures was calculated using the linear logarithmic relationship obtained. DPC 963 undergoes sublimation at appreciable rates at 150°C and above but this is not likely to pose a serious issue during the manufacturing process. Vapor pressure estimation using thermogravimetric analysis provided sufficient accuracy to be used as a fast, simple, and safe alternative to the traditional methods of vapor pressure determination.

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KEYWORDS: sublimation, vapor pressure, thermogravimetric analysis-infrared (TGA-IR)

INTRODUCTION

The nonnucleoside reverse transcriptase inhibitor (NNRTI) against human HIV-1 retrovirus, efavirenz, has been shown to be an effective component in the multidrug regimens in treating HIV-1-infected patients.[1] Second-generation NNRTIs with more potent activity against efavirenz-resistant HIV mutants have been identified.[2,3] (-)-4-Cyclopropylethynyl-5,6-difluoro-4-trifluoromethyl-3,4-dihydro-2(1H)-quinazolinone (DPC 963, **Figure 1**), a second-generation NNRTI with expanded spectrum of antiviral activity, is under development.

DPC 963 was crystalline with a melting point of 192°C determined by differential scanning calorimetry (DSC). DPC 963 drug substance used for safety and clinical studies was of at least 99% purity. Thermogravimetric analysis (TGA) showed very little weight loss when heated to 140°C, indicating the absence of a solvate or hydrate. However, upon further evaluation, TGA showed consistent weight loss of the drug substance when it was heated above 150°C. The amount of weight loss was larger than the total amount of residual solvent and water as determined by gas chromatography and Karl-Fischer Coulometric titration. In addition, this weight loss could not be accounted for by the volatile impurity in the drug substance. The purpose of this research is to investigate the possible sublimation process of DPC 963, and to better understand the impact of this observed weight loss during active pharmaceutical ingredient (API) manufacture and formulation development, especially the drying processes. TGA-infrared (IR) was used to characterize the vapor phase resulting from DPC 963 when heated above 150°C.[4]

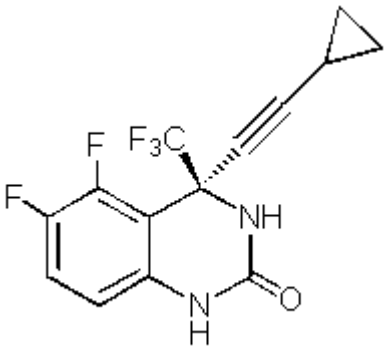

Figure 1. Chemical Structure of DPC 963.

MATERIALS AND METHODS

Materials

DPC 963 was prepared by the Chemical Process R&D department of DuPont Pharmaceuticals Co (Deepwater, NJ) following cGMP regulations. Reagent grade benzoic acid was purchased from JT Baker (Philipsburg, NJ). All solvents were high-performance liquid chromatography (HPLC) grade, and other reagents were analytical grade. The water was house-deionized water after passing through a Milli-Q plus ion-exchange cartridge system (Millipore Corp, Boston, MA) resulting in a specific resistance of greater than 18 MΩ-cm.

TGA-IR Study

Qualitative identification of the vapor phase components was made using a Fourier transform IR (FTIR) spectrometer coupled to a TGA instrument (E.I. Du Pont de Nemours, Wilmington, DE). A weighed sample of DPC 963 was placed in a quartz boat and positioned in the heating zone of the TGA apparatus inside a quartz tube. The tube was sealed under a nitrogen purge gas at a constant flow rate of 80 mL/min. The sample was heated from room temperature to 170°C at a heating rate of 10°C/min and held at 170°C for 30 minutes; then heated from 171°C to 185°C at a rate of 5°C/min and held for 5 minutes at 185°C. The sample weight was monitored throughout the experiment. During the experiment, the vapor phase was swept through a 20-cm IR gas cell, which was scanned continuously by the FTIR spectrometer. The FTIR spectrometer was operated at 4 cm^{-1} resolution with 34 scans combined to yield a data point (spectrum) every 30 seconds. The cell was maintained at a temperature of approximately 250°C to avoid condensation of higher boiling components. Spectra representing each heating segment were compared with the spectrum of untreated DPC 963. The vapor phase was also collected in a polyvinylfluoride bag, and the condensed material was analyzed by both HPLC and FTIR.

The chromatographic analysis was performed on an Alliance 2690 HPLC separation module (Waters Corporation, Boston, MA) using a 4.6 mm × 25 cm reverse-phase Zorbax R_x-C_8 column (Hewlett Packard, Wilmington, DE) with the temperature maintained at 25°C. The separation was achieved with an isocratic method using a mobile phase composed of acetonitrile:water (50:50, vol/vol) with 0.05% (vol/vol) trifluoroacetic acid at a flow rate of 0.8 mL/min. Ultraviolet detection was employed at 250 nm (Model 486 Tunable Absorbance Detector, Waters Corporation). Data acquisition was controlled by a VAX-based program, which also calculated the sample concentrations from a standard curve (Multichrom software, VG Instruments, Boston, MA).

Determination of Sublimation/Evaporation Rates

The sublimation/evaporation rate of DPC 963 at a given temperature was determined using isothermal TGA (TGA 2950, TA Instruments, Newark, DE). Data acquisition and analysis were achieved using thermal analyzer software (Thermal Analyst 5000, TA Instruments). A constant nitrogen gas purge at 80 mL/min was used during the experiments. The furnace was first heated rapidly to the desired temperature and maintained for 10 minutes with a nitrogen purge to flush the furnace space. The DPC 963 drug substance was then loaded quickly to minimize temperature decrease and the run initiated. The sample amount for each run was kept constant at 14.0 ± 0.5 mg and the temperature maintained constant during each experiment. At least 30% weight loss was monitored for each run to allow an accurate determination of the rate of weight change. The slope of the linear region of each TGA thermogram, which was the rate of sublimation/evaporation, was obtained using a linear regression model. The sublimation/evaporation rate of DPC 963 was determined over a temperature range of 150°C to 220°C.

Benzoic acid was used as a reference standard for vapor pressure estimation by TGA. The isothermal sublimation rates of benzoic acid were determined using the same method and the same instrumental configuration as DPC 963 over a temperature range of 40°C to 70°C.

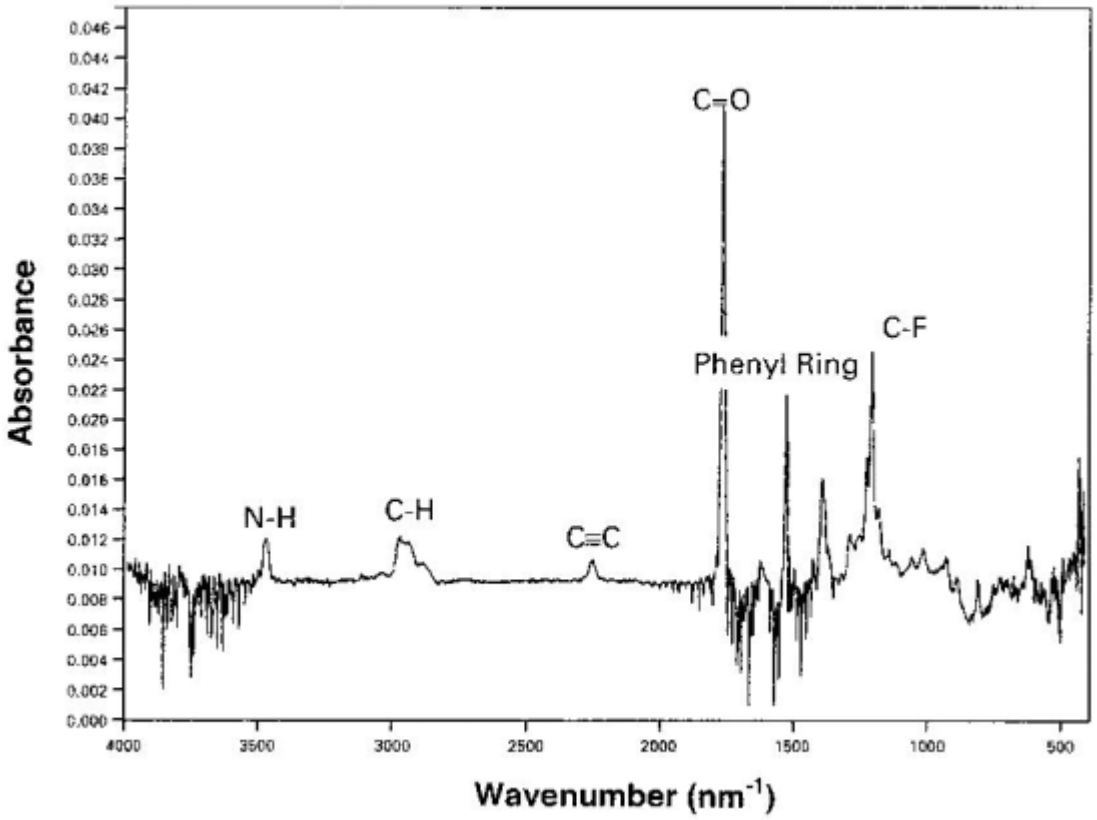

Figure 2. Chemical Structure of DPC 963.

Isolation and Characterization of the Condensed Material

Two types of condensed material from sublimation or evaporation of DPC 963 were collected from 2 sites around the furnace. Each material was further characterized by DSC, x-ray powder diffraction (XRPD), and IR spectrometry.

The thermal properties of DPC 963 and condensed material were analyzed by DSC (DSC 2920, TA Instruments) employing a heating rate of 10°C/min over a temperature range of 25°C to 300°C. Data analysis was achieved using thermal analyzer software (Thermal Analyst 5000, TA Instruments).

XRPD patterns for DPC 963 and the condensed material were obtained with a D8 ADVANCE Bruker x-ray diffractometer (Bruker, Karlsruhe, Germany) equipped with a scintillation counter and a graphite monochromator, soller slits, and fixed divergence and scattered-radiation slits. The radiation was CuK (α) (40 kV, 40 mA). Data were collected at room temperature from 2 to 60° 2θ with a step size of 0.02°, and the count time was 0.6 second per step. The slit widths were 1.0 mm for the divergence slits, 0.2 mm for the scattered-radiation slit, and 0.6 mm for the monochromator slit. The sample was prepared in a plastic Bruker sample holder with a specimen size of 25 mm in diameter and 1-mm thickness in a neat state without adhesives.

RESULTS AND DISCUSSION

TGA-IR Analysis

TGA coupled with FTIR detection provided a powerful tool to qualitatively determine the content of a vapor phase.[4] During the TGA-IR analysis, vapor phase of the DPC 963 sample was swept continuously, and a collective FTIR spectrum was generated every 30 seconds. From room temperature to 150°C, the FTIR spectra of the vapor phase indicated the presence of only carbon dioxide, moisture, and air. When heated from 150°C to 185°C, peaks characteristic of the functional groups present in DPC 963 were observed in the FTIR spectra (**Figure 2**). The functional groups such as C-F, phenyl ring, C≡C, N-H, and C-H in the IR spectra suggested the presence of either DPC 963 or compounds related structurally to DPC 963 in the vapor phase at temperature above 150°C. Presence of DPC 963 or

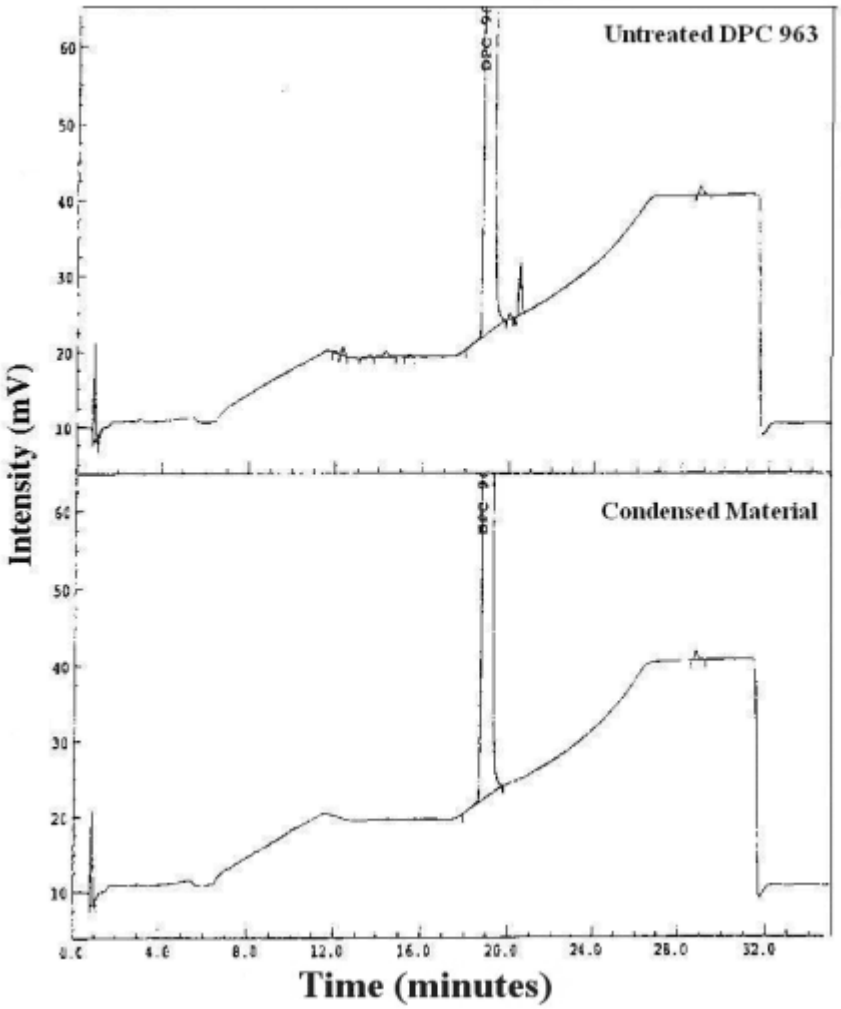

Figure 3. HPLC chromatograms of untreated DPC 963 and the condensed material.

related substance in the vapor phase could be due to either sublimation or thermal decomposition of DPC 963 drug substance.

To answer the question of sublimation versus thermal decomposition, the condensed material from the vapor phase was collected in a polyvinylfluoride bag. The condensed material and the remaining DPC 963 solid in the quartz boat were characterized by HPLC. Each sample was dissolved in acetonitrile:water mixture (50:50, vol/vol) and analyzed on HPLC. Both HPLC chromatograms showed a single major peak eluting at 19.3 minutes consistent with that observed with the untreated DPC 963 sample, and no degradation or impurity peaks were detected in the condensed material as shown in **Figure 3**. The percentage purity obtained based on HPLC peak area was 99.6% and 98.7% for the condensed material and the remaining DPC 963 sample, respectively, compared with a purity of 99.0% for the untreated DPC 963 drug substance. These results indicate that DPC 963 did not undergo thermal decomposition in the TGA-IR experiment, and the substance observed in the vapor phase was DPC 963 resulting from sublimation. In addition, a sample of DPC 963 was heated to 250°C using DSC and was analyzed by HPLC. The result was consistent with the other 2 samples, suggesting that DPC 963 did not undergo thermal decomposition below 250°C.

The DSC thermograms for both the condensed material and the remaining solids in the sample boat were also identical to that of the original DPC 963 drug substance as received. Close examination of the DSC thermogram between 150°C and 185°C revealed no thermal event in this temperature region, indicating that no thermal degradation occurred. Furthermore, purity

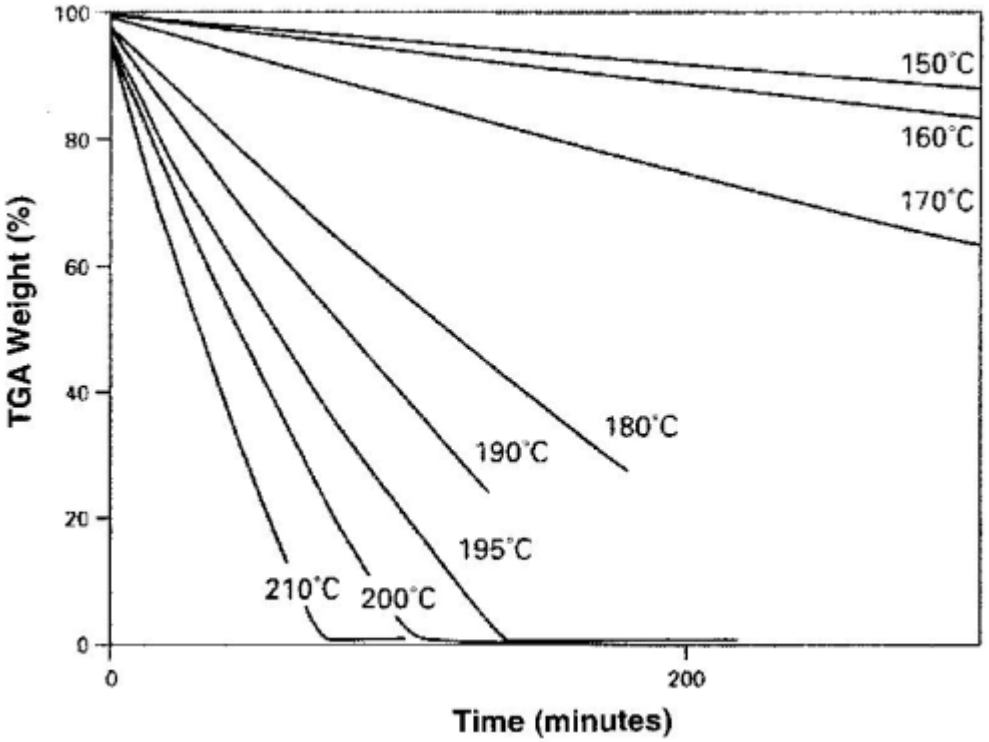

Figure 4. The representative weight-loss thermograms from isothermal thermogravimetric analysis of DPC 963 from 150°C to 220°C.

analysis on the melting endothermic transition of DPC 963 from 187°C to 196°C suggested a purity of 99%, consistent with the fact that no decomposition occurred below 250°C. These results indicate that the chemical entity in the vapor phase observed above 150°C was the result of sublimation rather than thermal decomposition, and DPC 963 sublimated at an appreciable rate at above 150°C.

Determination of Sublimation Rate

The rate of DPC 963 sublimation at a given temperature was determined by monitoring the rate of weight loss of DPC 963 by TGA. This method requires the sample to be at least 95% pure[5] and without substantial amount of residue solvent or other volatile impurities. Being 99% pure with little volatile impurities, the DPC 963 drug substance clearly satisfied the purity requirements.

Figure 4 shows a set of representative experimental time courses (TGA thermograms) depicting weight loss from 150°C to 220°C. From 150°C to 180°C, the thermograms, plotted weight loss versus time, were linear, which indicates that the sublimation followed apparent zero-order kinetics. Similarly, at temperatures above 200°C, the weight loss curves of DPC 963 were also linear and followed apparent zero-order kinetics. Since this temperature range was above the melting point of DPC 963, the weight loss was actually due to evaporation rather than sublimation. In the temperature region close to the melting point (185°C to 195°C), the weight loss thermograms became nonlinear, possibly due to premelt softening of the crystals and vaporization from a mixture of solid and liquid with a constantly changing ratio during melting. In this case, the rate of weight loss was a combination of sublimation and evaporation rates. This temperature range of nonlinear kinetics was consistent with the temperature span of the melting endotherm of DPC 963 observed by DSC, from 187°C to 196°C.

The zero-order rate of sublimation/evaporation at a given temperature, which was the slope of each isothermal TGA thermogram, was obtained using linear regression (**Table 1**). For the nonlinear weight loss data, the rate was determined from the initial 10% weight loss, which was relatively linear, but may not reflect the true rate over the entire time course. Thus, the rates from this temperature range (185°C-195°C)

Table 1. DPC 963 Sublimation Rate (<185°C), Evaporation rate (>200°C), and Estimated Vapor Pressure*

Temperature,°C	Sublimation/Evaporation Rate (SD), µg/min	Estimated Vapor Pressure (SD), Pa
150	4.80 (0.02)	7.6 (0.0)
160	10.11 (0.05)	13.9 (0.0)
170	20.85 (0.14)	25.0 (0.1)
180	50.26 (1.28)	51.4 (1.1)
200	133.50 (2.89)	114.4 (2.4)
210	195.43 (5.95)	156.2 (4.9)

*Rate of weight loss at each temperature was determined in triplicate.

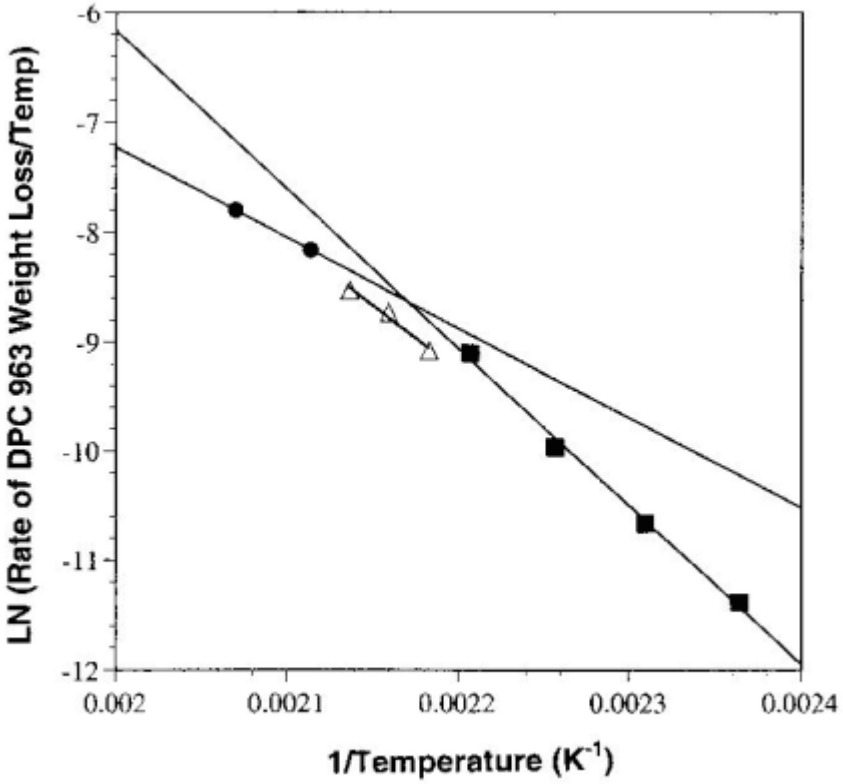

Figure 5. The Eyring plot for DPC 963 sublimation process (■) below the melting point (R^2 of 0.992), evaporation process (●) above the melting point (R^2 of 1.00), and the combination of sublimation and evaporation process (Δ) at temperatures close to the melting point (R^2 of 0.977). The solid lines represent the theoretical line fitted using the Eyring equation.

were not included in the calculation of thermodynamic parameters.

The rate of sublimation or evaporation obeys the Eyring equation (Equation 1) from which the enthalpy and entropy of each process can be calculated. The Eyring equation was fitted to the data and is shown in **Figure 5**.

$$\text{Ln (rate/T)} = -\Delta H/RT + \Delta S/R \quad (1)$$

T is the temperature, ΔH the enthalpy for the sublimation/evaporation process, and ΔS the entropy for this process. R is the molar gas constant. The sublimation enthalpy (from 150°C to 180°C) was 29 ± 2 kcal/mol, and the enthalpy of evaporation (from 200°C to 220°C) was 22 kcal/mol. Based on Hess's Law, the difference between the enthalpy of sublimation and evaporation is the heat of fusion, which is 7 ± 2 kcal/mol and in reasonably good agreement with the value, 5 kcal/mol, obtained by DSC analysis.

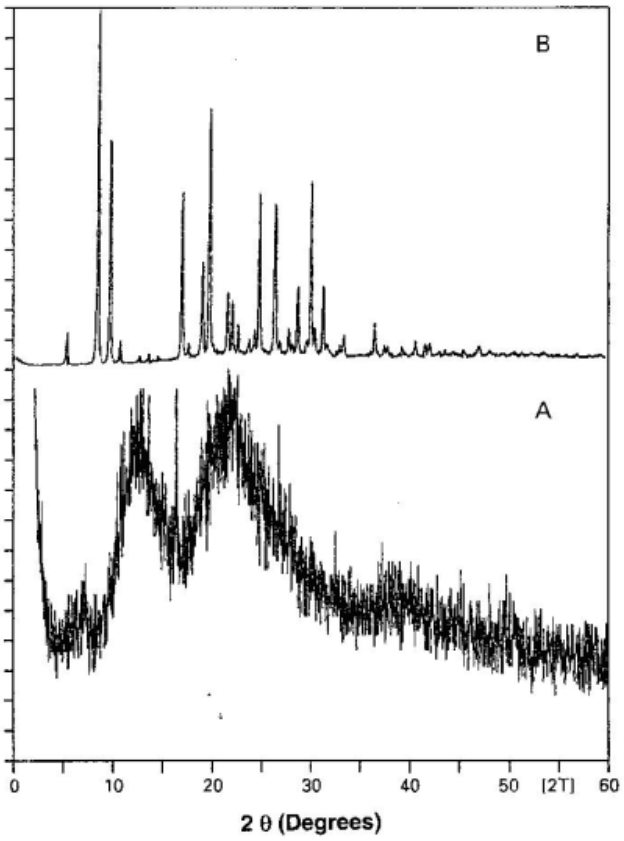

Figure 6. The x-ray powder diffraction pattern of the condensed material collected from (A) the upper position, and (B) from the lower position on the tube.

Characterization of Condensed Material

The DPC 963 vapor condensed at 2 different sites near the furnace and showed distinctively different physical appearance. The condensed material from both locations was collected separately and subjected to further characterization. The first location was on a metal plate above the furnace, and a fine powder was obtained and shown to be amorphous by XRPD, as shown in **Figure 6**. A more crystal-like material was obtained at a lower position, on a metal tube located in the furnace, and the crystallinity of this material was confirmed by XRPD to be the same crystalline form as the original DPC 963. These results were also confirmed by DSC analysis.

A possible cause for the 2 different physical forms may be the different temperature gradient generated between the heated DPC 963 sample and the 2 sites of condensation. The upper position was actually the bottom plate of the case housing the microbalance above the furnace and was being cooled by a heat-exchanger to room temperature to prevent overheating of the microbalance.[6] The lower position was on a 2-inch metal tube housing the microbalance hang-down wire and the thermocouple within the furnace. The sample pan was located approximately 1 inch below the metal tube where the sample was heated, and a constant temperature was maintained during each experiment. It is reasonable to assume that a greater temperature gradient existed between the sample pan and the upper position (metal plate) than that of the lower position (metal tube). Because of this greater temperature gradient, a higher degree of super-saturation was resulted by rapid cooling of the hot DPC 963 vapor to near room temperature when it encountered the plate. This high degree of supersaturation in the vapor phase likely led to rapid condensation to form many small particles, which lacked long-range molecular order and thus appeared amorphous. On the other hand, a shallower temperature gradient existed between the lower position and the sample, allowing slower cooling of the DPC 963 vapor and leading to a lower degree of supersaturation and slower nucleation and crystal growth, which ultimately resulted in a crystalline condensed material. These results demonstrate that the formation of solid material with different physical form from vapor phase is possible and can be controlled via temperature gradient.

The DSC thermograms of the untreated DPC 963 material and 2 types of condensed material are shown in **Figure 7**. The DSC thermogram of the amorphous material indicates a recrystallization process occurring at 95°C forming the same crystalline phase that melted at 192°C. The crystalline condensed material showed an identical DSC thermogram as the untreated DPC 963, suggesting the same crystalline structure. These results were confirmed by the XRPD analysis.

Vapor Pressure Estimation

Because DPC 963 undergoes sublimation at appreciable rates at temperatures above 150°C, the presence of DPC 963 in the atmosphere during drug substance manufacturing, especially during the drying process,

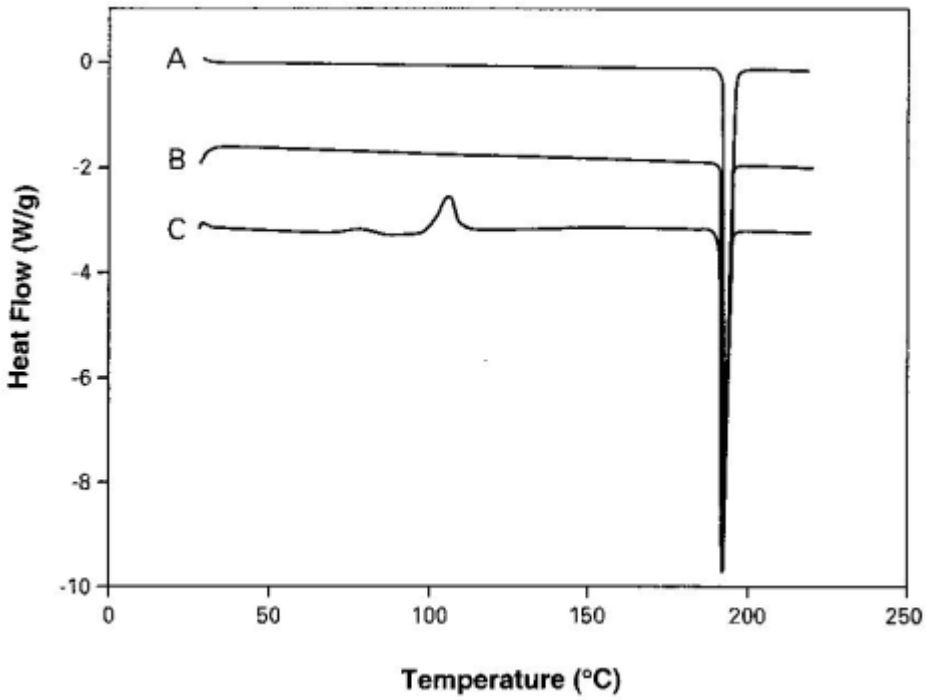

Figure 7. The differential scanning calorimetry thermograms for (A) the untreated DPC 963 drug substance, (B) the crystalline DPC 963 solids condensed from vapor, and (C) the amorphous DPC 963 solids condensed from vapor.

needs to be considered. Vapor pressure is a means to evaluate such environmental impact. Furthermore, the US Food and Drug Administration (FDA) requires the environmental fate and effects of a drug substance in the atmosphere be evaluated if the vapor pressure of the drug exceeds 1.33×10^{-5} Pa at room temperature.[7] The traditional methods for vapor pressure determination, especially for solids with very low vapor pressure under ambient conditions, are time consuming, labor intensive, and sometimes involve hazardous materials, such as radioactive compounds, to achieve high accuracy. A simple method with sufficient accuracy to evaluate the vapor pressure would be very beneficial.

In the past 20 years, Gückel and his coworkers[7] have conducted extensive studies on using thermogravimetric method to determine the vapor pressure. They suggested that the logarithm of sublimation/evaporation rate at a given temperature was linearly proportional to the logarithm of vapor pressure (Equation 2). This linear relationship between sublimation rate and vapor pressure is independent of the material used and the temperature range in which the experiments are carried out but is dependent on the specific instrumental system, experimental conditions, and sample containment procedure. With the high accuracy achieved by the microbalance used in the TGA today, a vapor pressure as low as 10^{-8} Pa can be determined in a wide temperature range from room temperature to as high as 800°C.[6,8] Therefore, in a vacuum-free environment, a simple thermogravimetric method provides sufficient accuracy to estimate vapor pressure of a drug substance by measuring the sublimation rate of uncompacted, as received, bulk active drug substance and by using the linear logarithmic relationship described in Equation 2.[9]

$$\text{Ln}(P) = a * \text{Ln}(k) + b \qquad (2)$$

P is the vapor pressure at a given temperature, and k is the rate of sublimation or evaporation at this temperature. Both a and b are constants specific to a given instrument and set of experimental conditions and procedures but independent of material and temperatures used.

In this study, benzoic acid was used as a reference compound to calibrate the TGA instrument and experimental conditions used because its vapor pressures have been accurately determined at different temperatures via multiple methods.[8,9] The sublimation rate of

Table 2. Experimentally Determined Sublimation Rate of Benzoic Acid Between 40°C and 70°C on the TGA System Used in This Study and the Published Vapor Pressure at Each Corresponding Temperature*

Temperature, °C	Sublimation Rate (SD), µg/min	Vapor Pressure†, Pa
40	0.36 (0.01)	0.910
45	0.76 (0.04)	1.546
50	1.01 (0.04)	2.582
55	2.57 (0.12)	4.245
65	7.93 (0.32)	10.985
70	12.57 (0.47)	17.306

*Rate of benzoic acid sublimation was at each temperature was determined in triplicates.
†The vapor pressures of benzoic acid were calculated using the data of Wiedemann.[8]

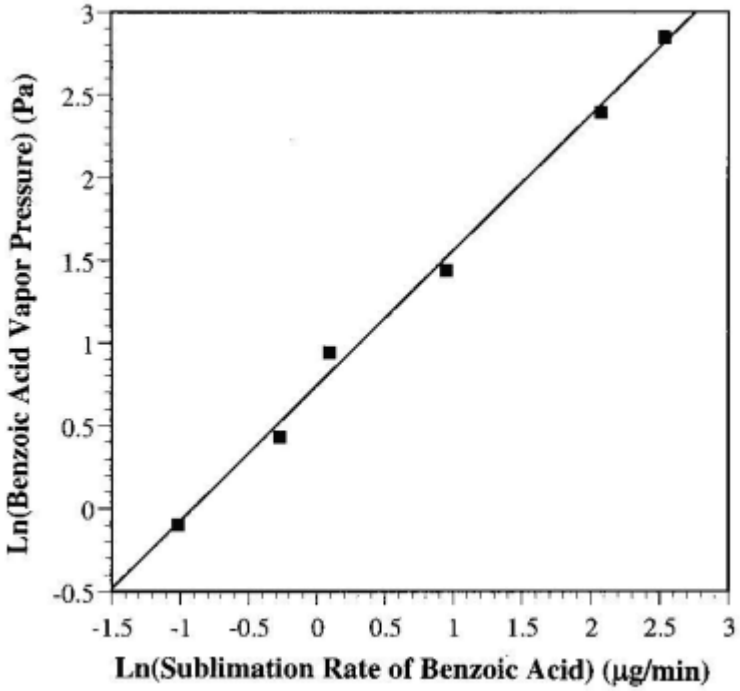

Figure 8. The linear logarithmic relationship between the sublimation rate of benzoic acid and the corresponding vapor pressure as reported in literature.[9] The theoretical line is obtained by fitting to Equation 2 and represents Equation 3 with a correlation coefficient (R^2) of 0.995.

benzoic acid from 40°C to 70°C was determined using identical procedure and experimental configuration as DPC 963, and the data are shown in **Table 2**. The sublimation rates of benzoic acid were plotted against the published vapor pressure at each temperature (**Figure 8**). Equation 2 was fitted to the data; and both constants, a and b, obtained with an R^2 value of 0.998, as shown in Equation 3.

$$\text{Ln (P)} = 0.817 * \text{Ln (k)} + 0.741 \quad (3)$$

Using Equation 3 and the measured sublimtion/ evaporation rate, the vapor pressure of DPC 963 at each

specific experimental temperature was calculated (**Table 1**). At 150°C, the estimated vapor pressure for DPC 963 was 7.6 Pa. The sublimation rate of DPC 963 at room temperature was too low to be determined by isothermal TGA but could be obtained by extrapolation from measured rates of sublimation at higher temperatures using the Eyring equation. This calculation assumed the enthalpy and entropy of sublimation were constant throughout the temperature range as long as DPC 963 remained in the same physical form. The sublimation rate at 25°C calculated using this method was 2.0×10^{-9} µg/min, which produced a vapor pressure of 1.6×10^{-7} Pa. This vapor pressure was much lower than the criterion of 1.33×10^{-5} Pa set by the FDA. Therefore, the environmental fate and effects of DPC 963 in the atmosphere need not be investigated at this point.

CONCLUSION

TGA-IR analysis is a powerful tool to qualitatively characterize the composition of the vapor phase of a pharmaceutically relevant substance. When used in combination with other thermal analytical techniques such as DSC, this method will yield useful information on processes such as thermal decomposition, desolvation of solvates/hydrates, and sublimation.

Both the sublimation and evaporation of DPC 963 followed apparent zero-order kinetics, and the rate of weight loss can be determined accurately by using isothermal TGA. Different physical forms, amorphous and crystalline, were obtained from condensation of the vapor phase, likely because of differences in temperature from the thermogradient.

In addition, sublimation/evaporation rates determined by isothermal TGA can be used to estimate vapor pressure of a given compound with sufficient accuracy. Compared with traditional methods of vapor pressure measurement, the thermogravimetric method provides a promising alternative that is easy to use, rapid, and requires only a small amount of drug substance.

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