Vapor Pressure and Enthalpy of Vaporization of Fentanyl

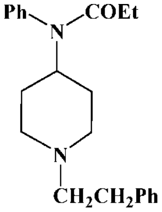
Pradeep K. Gupta,* Kumaran Ganesan, Pranav K. Gutch, Laxmi Manral, and Devendra K. Dubey

Synthetic Chemistry Division, Defence Research & Development Establishment (DRDE), Gwalior- 474002 (M. P.), India

This paper describes the application of thermogravimetry including conventional thermobalance and standard sample holders for the estimation of vapor pressure and related thermodynamic properties of a potent narcotic analgesic, fentanyl (CAS No. 437-38-7). For this study, benzoic acid was used as a reference material to calibrate the thermogravimetric analysis (TGA) instrument and experimental conditions used. The relationship between the isothermal sublimation rates of benzoic acid determined at different temperatures and the corresponding literature vapor pressure values was established, and the correlation equation thus obtained was used for the estimation of vapor pressure of fentanyl. By adopting this procedure, the vapor pressure of fentanyl was estimated at different temperatures from $T = (423.15 \text{ to } 493.15)$ K. Extrapolation of the measured data to $T = 298.15$ K gave the vapor pressure of subcooled fentanyl and estimated it to be $(4.6 \pm 2.7)\cdot 10^{-6}$ Pa. The corresponding solid phase vapor pressure of fentanyl was calculated to be $(5.9 \pm 4.7)\cdot 10^{-7}$ Pa after taking the enthalpy of fusion into consideration. Related thermodynamic properties, viz., enthaply of vaporization and normal boiling points, were also estimated from the vapor pressure–temperature curve.

Introduction

Fentanyl, *N*-(1-phenethyl-4-piperidinyl)propionanilide (**1**) (CAS No. 437-38-7), is a schedule II controlled substance, classified as a narcotic analgesic. It is the representative compound of the 4-anilidopiperidine class of narcotic analgesics and is characterized by very high analgesic potency, relatively short duration of action, and good overall safety margin during surgical anesthesia. It is chemically related to meperidine and is 50 to 100 times more potent than morphine.[1] It was introduced in clinical practice in the 1960s as an analgesic, and its application as an anesthetic agent represented a major increase in its potency in comparison with other contemporary opiate agonists.[2]



1

Fentanyl can be delivered to the human body through a variety of ways including oral intake in the form of a lollipop (Actiq), a transdermal patch (Duragesic), and inhalation. When administered through the inhalation route, an immediate anesthetic effect has been observed because of the fast absorption from the nasal mucosa and lung capillaries.[3] Owing to this effect, substantial efforts have been devoted to developing technologies that enable systemic delivery of fentanyl via inhalation.[4] These techniques were mostly based on a liquid aerosol approach, a dry powder approach, and generation of aerosols via thermal means.[3] Various physiochemical properties play a critical role in deciding its inhalation potential, and knowledge of these parameters is very crucial for the development of drug delivery technologies. Vapor pressure is one of the most important factors among them.

There are several techniques for the measurement of vapor pressure of low volatility chemicals which include the isoteniscope[5] Knudsen effusion[6,7] and gas saturation[8] methods. These methods, however, are time-consuming, are labor intensive, and sometimes involve hazardous materials such as radioactive compounds to achieve high accuracy. Moreover, these methods require great care to obtain accurate and reproducible results. There also exist various predictive schemes for the calculation of vapor pressure based on the group contribution approach.[9] These predictive schemes have been implemented in computer modeling software.[10,11] The vapor pressures obtained from predicative methods, however, can show significant deviations from experimental values and are often not reliable.[12]

Thermogravimetry has been known for the estimation of vapor pressure of compounds having low volatility. With this technique, vapor pressures as low as 10^{-8} Pa can be determined over a wide temperature range from room temperature to as high as 1000 K.[13] Thermogravimetry analysis (TGA) is used to measure the accelerated vaporization rates at elevated temperatures. It has been shown that the evaporation process follows zero-order kinetics, and the rate of mass loss of a substance under isothermal conditions due to vaporization remains constant provided the free surface area does not change.[14] Price and Hawkins suggested that it is possible to use thermogravimetry to determine the vapor pressures using the Langmuir equation for free evaporation.[12] Guckel et al. have measured the rate of volatilization of pesticides at ambient pressure by isothermal thermogravimetry.[15] Elder has used this technique for the determination of vapor pressure of pharmaceutical compounds with moderate accuracy.[16] Both Guckel[15] and Elder[16] have correlated the rate of mass loss with vapor pressure using the same behavior of a substance of known vapor

---

* Corresponding author. E-mail: pr_14@rediffmail.com. Fax: 91-751-2341148.

10.1021/je7005067 CCC: $40.75

pressure as a standard. Thus, the thermogravimetric method of vapor pressure determination has provided an alternative to traditional techniques that is easy to use, is rapid, and requires only a small amount of substance.

In the present paper, we describe the use of thermogravimetry for the estimation of vapor pressure, enthalpy of vaporization, and normal boiling point of fentanyl. To the best of our knowledge, no systematic studies have been carried out for the determination of vapor pressure and related thermodynamic properties of fentanyl. An extensive literature survey revealed that only two reports are available on the vapor pressure of fentanyl.[17,18] One of them[17] is based on the gas chromatographic determination of the vapor pressure of fentanyl which reported the vapor pressure value at $T = 298.15$ K only. The second report[18] calculated the vapor pressure of fentanyl at $T = 298.15$ K using the fragment constant method. However, the values determined by this method have shown deviations from experimental values.[12] Moreover, the temperature dependence of vapor pressure and related thermodynamic properties have not been reported.

Theory

According to the Langmuir equation (eq 1) for free evaporation in vacuo, the relationship between the rate of mass loss of a substance and its vapor pressure at a particular temperature is[19]

$$\frac{\mathrm{d}m}{\mathrm{d}t} = p\alpha\sqrt{\frac{M}{2\pi RT}} \tag{1}$$

where d*m*/d*t* is the rate of mass loss of the substance per unit area; *p* is the vapor pressure at absolute temperature *T*; *M* is the molecular weight of the effusing vapor; and *R* is the gas constant. The vaporization coefficient α is equated to 1 for evaporation in vacuo, but for a material volatilizing into a flowing gas stream at one atmosphere, it is not assumed to be unity. On rearrangement, eq 1 can be written as

$$p = \frac{\mathrm{d}m}{\mathrm{d}t} \cdot \sqrt{\frac{T}{M} \cdot \frac{1}{\alpha}} \cdot \sqrt{2\pi R} \quad p = kv \tag{2}$$

$$\ln p = \ln k + \ln v \tag{3}$$

and the calibration constant $k = 1/\alpha\sqrt{2\pi R}$ and the vaporization rate $v = (\mathrm{d}m/\mathrm{d}t)\sqrt{T/M}$.

Equations 2 and 3 imply that the rate of evaporation of a compound at a specific temperature follows zero-order kinetics and is directly proportional to its corresponding vapor pressure. The calibration constant *k* 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 and experimental configuration. A plot of ln *p* against ln *v* follows the same trend for a series of compounds with known vapor pressure, regardless of the chemical structure, provided that the sample does not associate in the solid, liquid, or gas phase. It allows the calibration constant *k* to be calculated from the graph, and by knowing the value of *k*, the vapor pressures of unknown materials can be found using eq 3.

The temperature dependence of the vapor pressure can be described by the Classius–Clapeyron equation (eq 4)

$$\frac{\mathrm{d}(\ln p)}{\mathrm{d}T} = \frac{\Delta_{\alpha}^{\beta}H}{RT^2} \tag{4}$$

where $\Delta_{\alpha}^{\beta}H$ is the molar enthalpy of vaporization/sublimation for liquids/solids, respectively. Over the limited temperature range, $\Delta_{\alpha}^{\beta}H$can be assumed to be constant, and the integrated form of the Clausius–Clapeyron equation can be written as eq 5

$$\ln p = B - \frac{\Delta_{\alpha}^{\beta}H}{RT} \tag{5}$$

Putting eq 5 in eq 3 gives

$$\ln v = B' - \frac{\Delta_{\alpha}^{\beta}H}{RT} \tag{6}$$

Thus, according to eq 5, the enthalpy of vaporization/sublimation can be obtained from the graph plotted between ln *p* (estimated from the experimental rate of vaporizations, eq 3) and reciprocal temperature (1/*T*). It is, however, often difficult to obtain good quality vapor pressure data over a wide temperature range to evaluate the temperature dependence of $\Delta_{\alpha}^{\beta}H$. After studying a large number of materials, Chikos et al.[20] recommended the following equations for conversion of enthalpy of vaporization/sublimation to a standard state ($T = 298.15$ K)

$$\Delta_{\mathrm{sub}}H(298.15\ \mathrm{K})/\mathrm{kJ\cdot mol^{-1}} = \Delta_{\mathrm{sub}}H(T/\mathrm{K}) + 0.0320(T/\mathrm{K} - 298.15) \tag{7}$$

$$\Delta_{\mathrm{vap}}H(298.15\ \mathrm{K})/\mathrm{kJ\cdot mol^{-1}} = \Delta_{\mathrm{vap}}H(T/\mathrm{K}) + 0.0540(T/\mathrm{K} - 298.15) \tag{8}$$

Practically useful vapor pressure of the substance at $T = 298.15$ K can be obtained by extrapolating the measured data to this temperature. However, the vapor pressure at $T = 298.15$ K actually represents the vapor pressure of a subcooled liquid rather than the solid phase vapor pressure. The latter can be determined after taking the entropy of fusion into consideration by the following equation[21]

$$\ln p = \ln p + \left(\frac{\Delta_{\mathrm{fus}}S}{R}\right)\left(1 - \frac{T_{\mathrm{m}}/\mathrm{K}}{T/\mathrm{K}}\right) \tag{9}$$

where p_{S} and p_{L} are the solid and the liquid phase vapor pressures, respectively; $\Delta_{\mathrm{fus}}S$ is the entropy of fusion at the melting temperature T_{m}; *R* is the ideal gas constant (8.314 $\mathrm{J\cdot K^{-1}\cdot mol^{-1}}$); and *T* is the temperature of interest (here 298.15 K). The factor $\Delta_{\mathrm{fus}}S/R$ has been empirically equated to 6.79 for the calculation of solid phase vapor pressure.[13,21,22] However, a more realistic value of $\Delta_{\mathrm{fus}}S/R$ could be obtained by differential scanning calorimetry (DSC).

It is also possible to estimate the boiling temperature (T_{b}) of the compound at normal atmospheric pressure by extrapolating the vapor pressure–temperature curve to 101325 Pa. However, use of this estimated boiling point for practical applications should be done carefully because the compound may undergo decomposition at this temperature.

Experimental Section

Resublimed benzoic acid and 99 % bis(2-ethylhexyl)phthalate (CAS No. 117-81-7) were obtained from Acros and used as received. Fentanyl (CAS No. 437-38-7) was synthesized as reported previously,[23] and its purity (> 98 %) was determined by chromatographic and spectroscopic analysis. The melting point of fentanyl was measured using DSC analysis which also confirmed the purity of the compound.

Thermogravimetric analysis was performed using a TA Instruments model TGA 2950 with a water-cooled furnace. The thermobalance was calibrated for temperature according to the method of Stewart, using indium, tin, bismuth, and lead.[24] The magnitude and linearity of the balance response was

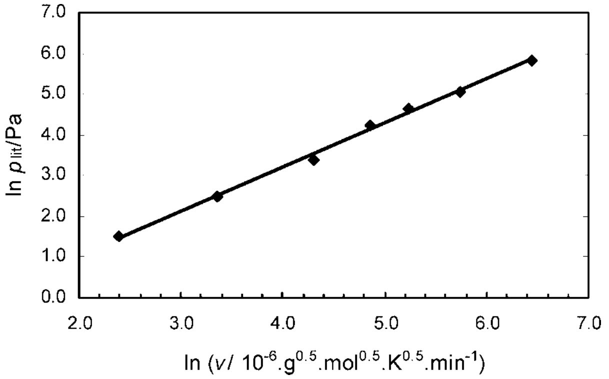


Figure 1. Correlation observed between ln v determined at T = (333.15 to 383.15) K and ln p_{lit}. The literature vapor pressures of benzoic acid (p_{lit}) at different temperatures were calculated using the parameters obtained from ref 29. The equation of the line was obtained by linear regression analysis of the graph and is given by ln p/Pa = (1.1 ± 0.1) ln v − (1.1 ± 0.1).

Table 1. Vapor Pressure of Bis(2-ethylhexyl)phthalate at T = (423.15 to 473.15) K Calculated from Experimental Rates of Vaporization (v) Determined at T = (423.15 to 473.15) K and Comparison of Calculated Values with Literature Values

T	v	p^a	$p_{lit}{}^b$
K	$10^{-6}g^{0.5}\cdot mol^{0.5}\cdot K^{0.5}\cdot min^{-1}$	Pa	Pa
423.15	19.2	8.0 ± 1.0	8.5
433.15	38.6	17.0 ± 1.0	17.1
443.15	70.4	32.6 ± 1.0	33.3
448.15	88.8	41.9 ± 1.0	44.7
453.15	134.1	65.5 ± 1.0	60.0
463.15	226.3	115.4 ± 1.0	108.0
473.15	354.1	187.4 ± 1.0	185.3

[a] Calculated using eq 10. [b] Ref 30.

checked with standard milligram masses. Samples were placed in tared aluminum cups (internal diameter 12.5 mm, depth 3 mm) of the type used for DSC measurements. For solid samples, the cup was filled completely with material which was then melted so that a known sample surface area was obtained while liquid samples were measured directly. The sample thermocouple was kept as close as possible to the surface of the specimen to accurately record its temperature without interfering with the operation of the balance. The furnace was purged with dry, oxygen-free nitrogen (flow rate: 90 mL·min^{-1} through the furnace and 10 mL·min^{-1} through the balance). The experiments were triplicated to ensure reproducibility.

Differential scanning calorimetry was performed using a TA instruments 2920 DSC under nitrogen (Flow rate: 10 mL·min^{-1}) to determine the melting point and enthalpy of fusion. The compound was encapsulated in hermetically sealed aluminum pans to prevent the loss of the material. The temperature of the furnace was increased from T = (323.15 to 423.15) K with rate of 10 K per minute. The instrument was calibrated for temperature and heat flow response according to the melting points and enthalpies of pure indium under the same conditions used to study the material under investigation.

Results

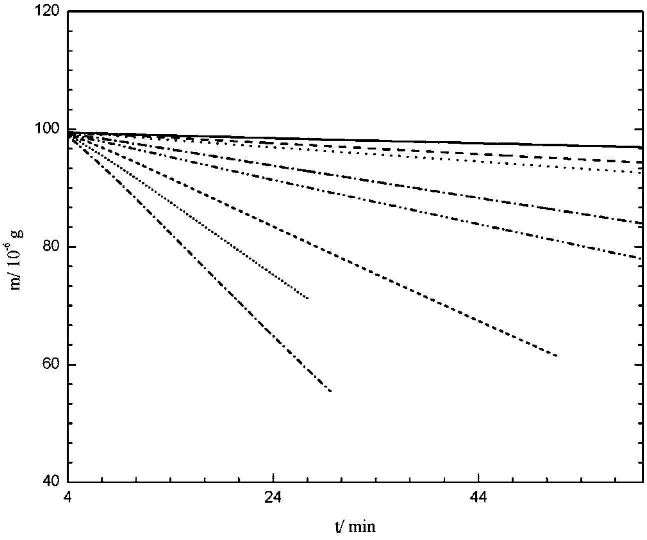


Figure 2. Isothermal TGA thermograms obtained by monitoring the mass loss of fentanyl with respect to time at different temperatures ranging from T = (423.15 to 493.15) K. The corresponding rates of vaporization of fentanyl at these temperatures were obtained from the slope of each thermogram which were used to calculate the vapor pressures of fentanyl using eq 10. −, 423.15 K; − − −, 433.15 K; • • • •, 443.15 K; −•−•, 453.15 K; -••-••-, 63.15 K; **---,** 473.15 K; ••••, 483.15 K; **-•-•**, 493.15 K.

For this study, benzoic acid was used as a reference compound to calibrate the TGA instrument and experimental conditions used. It has been recommended as a calibration and test material and used extensively as a standard for combustion and adiabatic calorimetry.[25] It has also been used a reference standard for vapor pressure estimation of various compounds by TGA.[12,16,26,27] During the present course, isothermal rates of sublimation for benzoic acid were determined at T = (333.15 to 383.15) K. The fact that the sublimation of benzoic acid followed the zero-order kinetics was confirmed by plotting a semilogarithmic graph between sublimation rate (ln v) and 1/T. The experimental enthalpy of sublimation of benzoic acid (88.8 ± 2.0) kJ·mol^{-1} was obtained from the slope of the graph and found in good agreement with literature values of (89.7 ± 1.0) kJ·mol^{-1}.[28] A calibration curve (Figure 1) was obtained by plotting a double logarithmic graph between ln v at a particular temperature and corresponding literature vapor pressure ln p_{lit}.[29] The correlation equation (eq 10) was then obtained by the linear regression analysis of the graph (r^2 = 0.99, SD = 0.105)

$$\ln p/\mathrm{Pa} = (1.1 \pm 0.0)\ln(v/10^{-6}g^{0.5}\cdot \mathrm{mol}^{0.5}\cdot \mathrm{K}^{0.5}\cdot \mathrm{min}^{-1}) - (1.1 \pm 0.1) \quad (10)$$

Equation 10 was a general equation which could be used for the estimation of vapor pressure of any compound at different temperatures provided its rates of vaporizations/sublimations have been determined from TGA analysis. However, before applying this method for fentanyl, the authenticity of eq 10 was checked by determining the vapor pressure of bis(2-ethylhexyl)-phthalate and comparing the results with the published values.[30] Bis(2-ethylhexyl)phthalate has been used as a reference compound for the measurement of vapor pressure,[31] and its vapor pressure has been determined accurately by different methods.[30,32] The vaporization rates of bis(2-ethylhexyl)phthalate were determined at different temperatures, and corresponding vapor pressure was determined using eq 10 (Table 1). Good agreement between estimated and literature values of vapor pressure of bis(2-ethylhexyl)phthalate proved the correctness of the method.

The vapor pressure of the fentanyl was calculated using a similar procedure adopted for bis(2-ethylhexyl)phthalate. The rates of vaporization of fentanyl were determined by monitoring the rate of weight loss by TGA using an identical procedure and under similar experimental configurations as used earlier. Figure 2 shows a set of representative experimental time courses

Table 2. Vapor Pressure of Fentanyl at T = (423.15 to 493.15) K Calculated from Experimental Rates of Vaporization (v) Determined at T = (423.15 to 493.15) K

T	v	p^a
K	$10^{-6}\text{g}^{0.5}\cdot\text{mol}^{0.5}\cdot\text{K}^{0.5}\cdot\text{min}^{-1}$	Pa
423.15	3.5	1.3 ± 0.9
433.15	9.3	3.6 ± 0.9
443.15	16.7	6.9 ± 0.9
453.15	34.2	14.9 ± 1.0
463.15	49.0	22.0 ± 1.0
473.15	89.3	42.2 ± 1.0
483.15	149.2	73.5 ± 1.0
493.15	204.4	103.3 ± 1.0

[a] Calculated using eq 10.

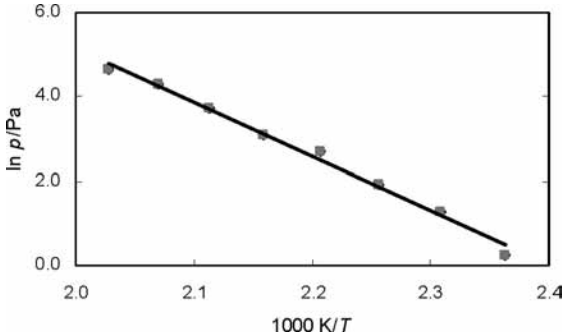


Figure 3. Correlation obtained between the vapor pressure of fentanyl calculated using eq 10 at T = (423.15 to 493.15) K and 1/T. The equation of the line obtained by linear regression analysis is given by ln p/Pa = (31.0 ± 1.1) – (12898.1 ± 502.8) T^{-1}/K^{-1}.

(TGA thermograms) depicting weight loss at T = (423.15 to 493.15) K at 10 K increments. In this temperature range, the thermograms (a plot of weight loss vs time) were linear which indicated that the vaporization followed zero-order kinetics. No reliable measurements on sublimation rates of fentanyl (solid phase vaporizations) could be made because of very small weight loss. The zero-order rates of evaporation at different temperatures were obtained from the slope of isothermal TGA thermograms. The vapor pressure of fentanyl at each specific experimental temperature was then calculated from measured evaporation rates using eq 10 (Table 2). The calculated vapor pressure values of fentanyl were plotted against 1/T to get a linear curve (Figure 3, r^2 = 0.99, SD = 0.156). The correlation equation corresponding to the linear least-squares curve fit of these data was

$$\ln p/\text{Pa} = (31.0 \pm 1.1) - (12898.1 \pm 502.8)T^{-1}/\text{K}^{-1} \tag{11}$$

The coefficients of the equation could be used to estimate the vapor pressures of fentanyl at different temperatures. Generally, the vapor pressure of a compound is reported at T = 298.15 K. For fentanyl, it could be calculated by extrapolating the experimental vapor pressure data outside of the measured region and was found to be (4.6 ± 2.7)$\cdot 10^{-6}$ Pa. However, this estimated vapor pressure is actually the vapor pressure of a subcooled liquid. The corrected solid phase vapor pressure of fentanyl at T = 298.15 K could be obtained using eq 9. The entropy of fusion ($\Delta_{\text{fus}}S$) for fentanyl was determined by DSC analysis (Figure 4) and found to be (84.0 ± 8.4) J$\cdot$K$^{-1}\cdot$mol^{-1} at its melting temperature (T_{m} = 358.30 K). Hence $\Delta_{\text{fus}}S$/R was calculated to be 10.1 ± 1.0, and from eq 9, the solid phase vapor pressure of fentanyl at T = 298.15 K was calculated to be (5.9 ± 4.7)$\cdot 10^{-7}$ Pa.

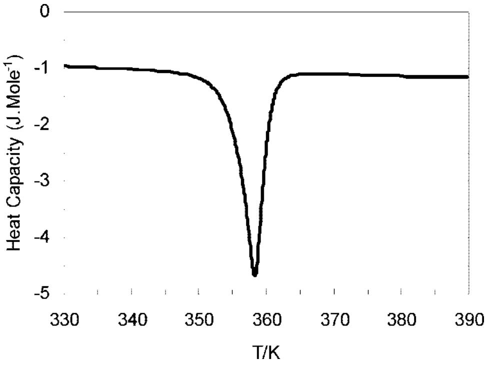


Figure 4. Differential scanning calorimetric (DSC) graph of fentanyl obtained by measuring heat flow between T = (323.15 to 423.15) K. It revealed the enthalpy of fusion to be (30.10 ± 3.00) kJ$\cdot$mol^{-1}.

Table 3. Liquid Phase Vapor Pressure (p_{L}), Solid Phase Vapor Pressures (p_{S}), and Enthalpy of Sublimation ($\Delta_{\text{sub}}H$) at T = 298.15 K and Normal Boiling Point (T_{b}) of Fentanyl

p_{L}	p_{S}	$\Delta_{\text{sub}}H$	T_{b}
Pa	Pa	kJ$\cdot$mol^{-1}	K
(4.6 ± 2.7)$\cdot 10^{-6}$	(5.9 ± 4.7)$\cdot 10^{-7}$	(144.6 ± 7.2) kJ$\cdot$mol^{-1}	(663.7 ± 49.5) K

Following eq 5, the enthalpy of vaporization ($\Delta_{\text{vap}}H$) of fentanyl, obtained from the slope of the plot of ln p vs 1/T (Figure 3), was found to be (107.2 ± 4.2) kJ$\cdot$mol^{-1} at the mean temperature of T = 458.15 K. On the other hand, the DSC analysis of fentanyl revealed its enthalpy of fusion to be (30.1 ± 3.0) kJ$\cdot$mol^{-1}. The sublimation enthalpy of fentanyl, calculated from these data, was corrected to T = 298.15 K using eq 7 and was found to be (144.6 ± 7.2) kJ$\cdot$mol^{-1}.

It is also possible to estimate the boiling point at normal atmospheric pressure (T_{b}) of fentanyl by extrapolating the vapor pressure vs temperature curve until the pressure is 101325 Pa (atmospheric pressure). For fentanyl, it was found to be (663.7 ± 49.5) K. All the thermodynamic data are presented in Table 3.

Conclusions

This work reports the vapor pressures and related thermodynamic properties, viz., enthalpy of sublimation and normal boiling point of fentanyl. These parameters were estimated from its isothermal rates of vaporization by making use of the Langmuir equation. Although this approach of vapor pressure determination does not take the effect of heat transfer and mass transfer phenomenon into consideration, it still provides a simplified and fast method for a preliminary screening of the vapor pressure of narcotic analgesics like fentanyl. Because these type of compounds are widely used as drugs of abuse, understanding the vapor pressure properties of these drugs is significant when attempting to develop the air monitoring equipment for their vapor detection. Moreover, fentanyl is also being used in medical practice as a potent analgesic and anesthetic, and knowledge of these thermodynamic data is critical for understanding and modeling the thermal aerosol formation of fentanyl which in turn is required for the development of its aerosol delivery system.

Acknowledgment

We sincerely thank Dr. R. Vijayaraghavan, Director, Defence Research and Development Establishment, Gwalior, for his keen interest and encouragement.

Supporting Information Available:

Details of all the experimentally determined data are available as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

Literature Cited

(1) Kudzma, L. V.; Severnak, S. A.; Benvenga, M. J.; Ezell, E. F.; Ossipov, M. H.; Knight, V. V.; Rudo, F. G.; Spencer, H. K.; Spaulding, T. C. 4-Phenyl- and 4-heteroaryl-4-anilidopiperidines. A novel class of analgesic and anesthetic agents. *J. Med. Chem.* **1989**, *32*, 2534–2542.

(2) Janssen, P. A. J. 1-Aralkyl-4-(N-aryl-carbonylamino)-piperidines and related compounds, US Patent, 1965, 3,164,600.

(3) Rabinowitz, J. D.; Wensley, M.; Lloyd, P.; Myers, D.; Shen, W.; Lu, A.; Hodges, C.; Hale, R.; Mufson, D.; Zaffaroni, A. Fast onset medications through thermally generatedaerosols. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 769–775.

(4) Mather, L. E.; Woodhouse, A.; Ward, M. E.; Farr, S. J.; Rubsamen, R. A.; Eltherington, L. G. Pulmonary administration of aerosolised fentanyl: pharmacokinetic analysis of systemic delivery. *Br. J. Clin. Pharmacol.* **1998**, *46*, 37–43.

(5) *American Society for Testing and Materials Annual Book of Standards, Part 24*; American Society for Testing and Materials: Philadelphia, PA, 1978; p 740.

(6) Thomson, G. W. *Techniques of organic chemistry*, 3rd ed.; Weissberger, A., Ed.; Interscience: New York, 1959; *Vol. 1, part 1,* Chapter IX, p 409.

(7) Thomson, G. W.; Douslin, D. R. *Techniques of chemistry*; Weissberger, A., Rossiter, B. W., Eds.; Wiley Interscience: New York, 1971; *Vol. 1, part 1*, Chapter II, p 23.

(8) Spencer, W. F.; Clith, M. M. Vapor density of dieldrin. *Environ. Sci. Technol.* **1969**, *3*, 670–674.

(9) Lyman, W. J.; Reehl, W. F.; Rosenblatt, D. H. *Handbook of Chemical Property Estimation Methods*; American Chemical Society: Washington DC, 1990; pp 15-1–15-29..

(10) Campanella, E. A. A vapor pressure equation for heavy compounds. *Chem. Eng. Technol.* **1997**, *20*, 101–107.

(11) Molecular Modelling Pro; ChemSW, Inc.: Fairfield, CA. http://www.chemsw.com.

(12) Price, D. M. Vapor pressure determination by thermogravimetry. *Thermochim. Acta* **2001**, *367–368*, 253–262.

(13) Price, D. M.; Hawkins, M. Calorimetry of two dispersed dyes using thermogravimetry. *Thermochim. Acta* **1998**, *315*, 19–24.

(14) Dollimore, D. A breath of fresh air. *Thermochim. Acta* **1999**, *340–341*, 19–29.

(15) Guckel, W.; Kastel, R.; Lewerenz, J.; Synnatschae, G. A method for determining the volatility of active ingredients used in plant protection. Part III: The temperature relationship between vapour pressure and evaporation rate. *Pestic. Sci.* **1982**, *13*, 161–168.

(16) Elder, J. P. Sublimation measurements of pharmaceutical compounds by isothermal thermogravimetry. *J. Therm. Anal.* **1997**, *49*, 897–905.

(17) Meng, Y.; Lichtman, A. H.; Bridgen, D. T.; Martin, B. R. Inhalation studies with drugs of abuse. NIDA monograph; Vol. 173, 201–224. www.drugabuse.gov/pdf/Monographs/Monograph173/201-224_Meng, pdf.

(18) Lyman, W. J. *Environment Exposure from Chemicals*; Neely, W. B., Blau, G. E., Eds.; CRC press: Boca Raton, R. L., 1985; *Vol. I*, pp 13–48..

(19) Langmuir, I. The Vapor Pressure of Metallic Tungsten. *Phys. Rev.* **1913**, *2*, 329–342.

(20) Chickos, J. S.; Hesse, D. G.; Liebman, J. F. A group additivity approach for the estimation of heat capacities of organic liquids and solids at 298 K. *Struct. Chem.* **1993**, *4*, 261–269.

(21) Mackay, D.; Bobra, A.; Chan, D. W.; Shiu, W. Y. Vapor pressure correlations for low volatility environmental chemicals. *Environ. Sci. Technol.* **1982**, *16*, 645–649.

(22) Bidleman, T. F. Estimation of vapor pressure for nonpolar organic compouns by capillary gas chromatography. *Anal. Chem.* **1984**, *56*, 2490–2496.

(23) Gupta, P. K.; Ganesan, K.; Pande, A.; Malhotra, R. C. A convenient one pot synthesis of fentanyl. *J. Chem. Res.* **2005**, 452–53.

(24) Stewart, L. N. *Proc. 3rd Toronto Symp. Thermal Anal.*; McAdia, H. G., Ed.; Chemical Institute of Canada: Toronto, 1969; p 205.

(25) Good, W. D.; Smith, N. K. Enthalpies of combustion of toluene, benzene, cyclohexane, cyclohexene, methylcycolpentane, 1-methylcyclopentene, and n-hexane. *J. Chem. Eng. Data* **1969**, *14* (1), 102–106.

(26) Xie, M.; Ziemba, T. M.; Maurin, M. B. Sublimation characterization and vapor pressure estimation of an HIV nonnucleoside reverse transcriptase inhibitor using thermogravimetric analysis. *AAPS PharmaSciTech* **2003**, *4* (2), 23.

(27) Price, D. M.; Bashir, S.; Derrick, P. R. Sublimation properties of x,y-dihydroxybenzoic acid isomers as model matrix assisted laser desorption ionization (MALDI) matrices. *Thermochim. Acta.* **1999**, *327*, 167–171.

(28) Sabbah, R.; Xu-wu, A.; Chickos, J. S.; Leitao, M. L. P.; Roux, M. V.; Torres, L. A. Reference materials for calorimetry and differential thermal analysis. *Thermochim. Acta* **1999**, *331*, 93–204.

(29) *CRC Handbook of Chemistry and Physics*, 71st ed.; Lids, D. R., Ed.; CRC Press: USA, 1990–91; pp 5–87..

(30) Yaws, C. L. *Chemical properties handbook; Physical thermodynamic, environmental, Transport, safety and health related properties for organic and inorganic chemicals*; McGraw Hill: New York, 1999; pp 159–179..

(31) Donovan, S. F. New method for estimating vapor pressure by the use of gas chromatography. *J. Chromatogr. A* **1996**, *749*, 123–129.

(32) Hinckley, D. A.; Bidleman, T. F.; William, T. F. Determination of vapor pressure for nonpolar and semipolar organic compounds from gas chromatographic retention data. *J. Chem. Eng. Data* **1990**, *35*, 232–237.

Received for review August 1, 2007. Accepted January 8, 2008.

JE7005067