

## THE VAPOR PRESSURES OF TOPIRAMATE, NAPHTHALENE AND BENZOIC ACID


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**ABSTRACT:** The vapor pressures of topiramate, naphthalene and benzoic acid were determined at ambient temperature conditions using a gas saturation technique with gravimetric analysis in order to meet the requirements of an NDA submission. Naphthalene and benzoic acid were used as reference compounds to validate the methodology and qualify the apparatus. Gravimetric analysis, measuring the mass vaporized, was used rather than chemical analysis because it was easier. The apparatus was designed to control the temperature and flow rates of nitrogen, accurately measure the total volume of gas, allow simultaneous determinations of three samples. The sample capacity was 6 to 7 g. The mass of the sample holder was measured at several intervals to determine the mass lost to vaporization. The vapor pressures were calculated from the ideal gas law. The data were analyzed by plotting the vapor pressure vs. total gas flow for individual and combined flow rates. Three phases were identified, a pre-equilibrium, equilibrium, and post-equilibrium phase. Plots from the combined flow rates made it easier to identify the equilibrium phase.

The reported vapor pressures for topiramate, naphthalene and benzoic acid are the calculated mean of the values from the equilibrium phase. They are topiramate= $3.84 \times 10^{-6}$  Torr at 21.5°C to 25.0°C; naphthalene= $6.07 \times 10^{-2}$  Torr at 22.2°C to 23.5°C (lit= $6.28 \times 10^{-2}$  Torr calculated and  $8.21 \times 10^{-2}$  Torr experimental at 25°C); and benzoic acid= $6.09 \times 10^{-4}$  Torr at 22.0°C to 24.4°C (lit= $8.86 \times 10^{-4}$  Torr experimental at 21.4°C).

**Key words:** Gas saturation; Gravimetric analysis; Pre-equilibrium; Equilibrium; Post-equilibrium

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## INTRODUCTION

Topiramate (Figure 1) is a drug with anti-convulsants activity. When the NDA of this compound was originally filed, it was required to contain an Environmental Assessment (21 CFR Part 25.31a). At that time, the vapor pressure was one of several physical-chemical properties used to predict the environmental fate of the compound.

The vapor pressures of topiramate and two reference compounds, naphthalene and benzoic acid, were determined using a gas saturation technique modeled after a procedure described by (Rasavi,1986) that uses gravimetric analysis rather than chromatographic analysis to quantitate the amount of compound lost by vaporization. The gravimetric technique was selected because it simplified the determination.

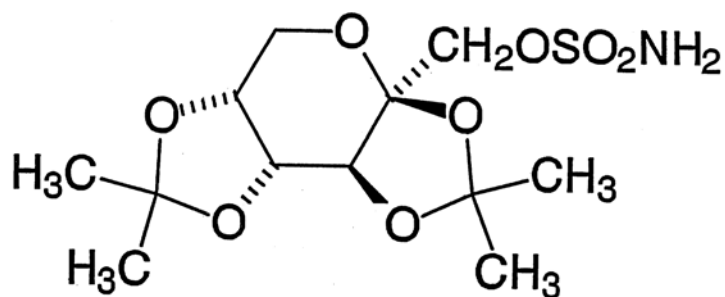


Figure 1. Topiramate.

The alternative is chemical analysis which requires collection of the vaporized compound from the effluent onto a column, desorption or extraction, appropriate dilution and chemical quantitation. For topiramate, quantitation requires capillary chromatography with refractive index detection because topiramate lacks a chromophore. Naphthalene and benzoic acid were selected as reference standards because of their availability, relative safety and their known vapor pressures. Wiedemann (Wiedemann HG (1972) reported two vapor pressures for naphthalene at 25°C of  $8.21 \times 10^{-2}$  Torr (experimental) and  $6.28 \times 10^{-2}$  Torr (calculated) and an experimental vapor pressure for benzoic acid at 21.4°C of  $8.86 \times 10^{-4}$  Torr.

## EXPERIMENTAL

A schematic of the experimental apparatus is presented in Figures 2 and 3. Nitrogen gas was passed through a moisture trap and a 50 ft coil of 1/4 in OD type 316 stainless steel tubing. The coil was connected to a stainless steel “cross” fitting which serves as a manifold and splits the nitrogen flow into three separate streams. Each of the streams was directed through 1/4 in OD type 316 stainless steel tubing to a gas flow controller (Omega FMA 116 Mass Flow Controller) and one channel of a five channel microprocessor totalizer (Omega FMA-5DV). A “quick connector” and short 1/4 in OD stainless steel “el” were used to connect the stainless steel gas lines to the sample holder (Figure 3). The sample holder was fashioned from a 4 in length of 0.035 in wall 0.55 in OD type stainless steel tube. Ferrules, glass wool and two stainless steel unions were added at the ends. Tygon tubing fastened by a clamp to the effluent side of the sample holder served as a vent.

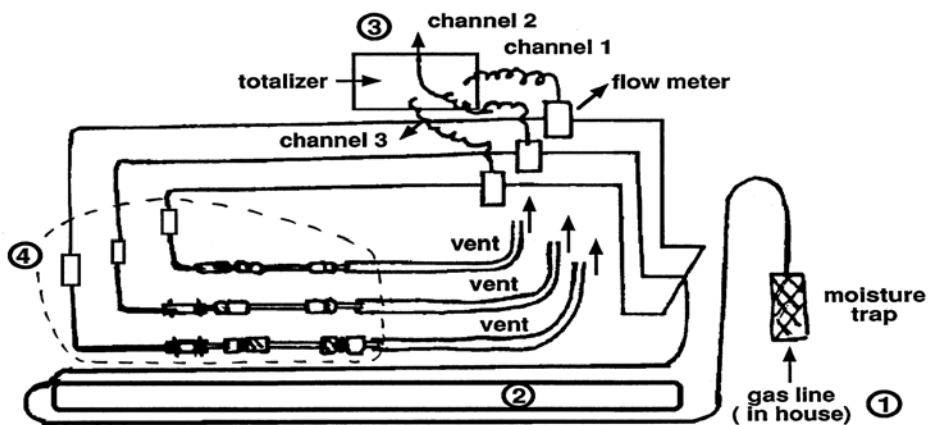


Figure 2. Experimental Apparatus Schematic.

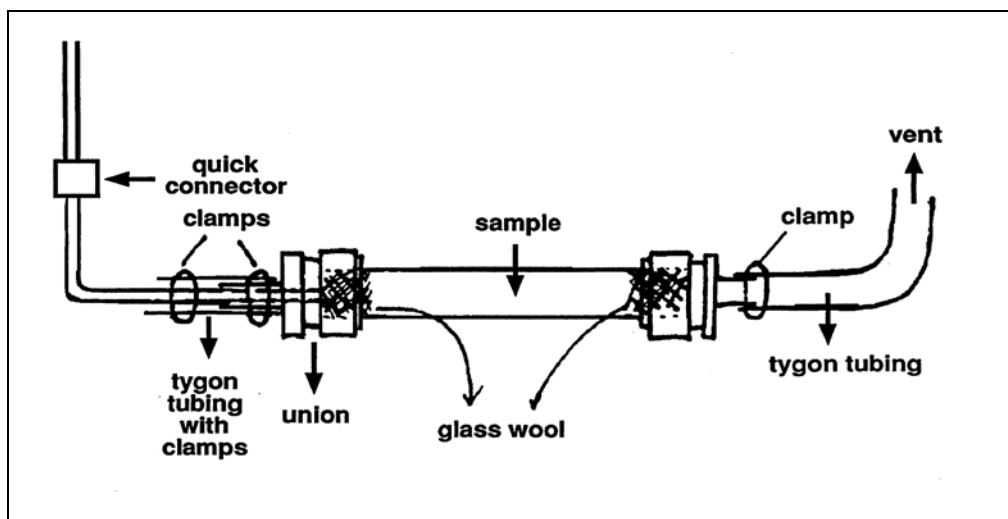


Figure 3. Experimental Apparatus Showing Enlarged View of Sample Holder

The 50 ft coil, manifold and sample holders were immersed in a tank containing Styrofoam peanuts, to insulate and control the temperature at ambient room temperature. A bath containing Styrofoam peanuts was used rather than water or oil because it was easier to keep the sample tubes dry and free of dust or oil. The system was tested for leaks prior to use by replacing the Styrofoam with water, operating the system and observing for bubbles. A glass thermometer was inserted into the Styrofoam mass and the temperature was recorded daily. The instrument was used over a 9 month period during which the temperature in the Styrofoam bath varied between 19.8°C and 25.0°C. The vapor pressure determinations required from two weeks to five months for completion. The temperature used for each calculation of the vapor pressure was the mean temperature for the measurement period.

The capacity of the sample holder (Figure 3) is ca. 6 to 7 g, and the combined weight of the sample and sample holder is ca. 155g. The Omega flow controller/totalizer system was factory calibrated. The rate of flow could be set and controlled within the range 1 to 1000 mL/min. The totalizer measured the total volume of gas flow in increments of 1 L and the total elapsed time in increments of 0.01 hours. A laboratory balance (Sartorius Model 1602 MP) with four decimal place accuracy was used for all weighings. Care was taken to remove the dust from the sample holder before weighing's. However, there was very little dust from the Styrofoam. Weighing errors were further reduced by wrapping the sample holder in aluminum foil while it was in the Styrofoam bath and by equilibrating the sample holder in a desiccator for 5 to 10 min before weighing.

Approximately 7 g of sample, naphthalene, benzoic acid or topiramate, were packed in each of three sample tubes. The sample tubes were weighed, attached to the apparatus and checked for leaks with the gas flowing. The sample tubes were then removed, dried, reweighed, and reattached to the apparatus. At periodic intervals, the flow of nitrogen was discontinued and the sample tube was removed, placed in a desiccator for 5 to 10 min before weighing, and the cumulative volume of gas was recorded. In some instances the determination was resumed.

The vapor pressure was calculated from the ideal gas law equation,

$$P = \frac{mRT}{(MW)(V)}$$

Where,

P=The vapor pressure, Torr

m=The mass (weight) loss, g

MW=The molecular weight of naphthalene=128.17; g mole<sup>-1</sup>

The molecular weight of benzoic acid=122.12; g mole<sup>-1</sup>

The molecular weight of topiramate=339.36; g mole<sup>-1</sup>

V=The cumulative volume obtained from the totalizer at each interval, L

R=The ideal gas constant, 0.082056 L atm K<sup>-1</sup> mole<sup>-1</sup>

T=The absolute temperature, K

## NAPHTHALENE

Both naphthalene and benzoic acid were ACS certified grade. The determination of the vapor pressure of naphthalene was initiated using three flow rates, 260, 400 and 800 mL/min. The sample holders were removed and weighed at 2 to 4 day intervals, at which time experimental vapor pressures were calculated. The 800 mL/min rate was discontinued after 9,792 L, and replaced with a rate of 500 mL/min because the successive (a) calculated vapor pressures at 800 mL/min declined linearly and (b) the sample weights were being reduced 17, 38 and 56% suggesting that the effluent vapor was not saturated with naphthalene. The total volumes of nitrogen gas from all four flow rates were between 717 to 12,279 L. The temperature range was 22.2°C to 23.5°C.

## BENZOIC ACID

The benzoic acid vapor pressure determination was initiated using 60, 400, and 900 mL/min flow rates. The first vapor pressure calculations were made after 3 and 7 days. The sample holders were reattached and the determination was continued for another 7 days. The flow rates in the 400 and 900 mL/min sample holders were reduced to 32 and 152 mL/min, respectively, and the 60 mL/min determination was extended to 14 days. The temperature range was 22.0°C to 24.4°C.

## TOPIRAMATE

The initial flow rates were 120, 400 and 900 mL/min. After about 1 month, the sample tubes were disconnected and their weights were recorded. The 900 mL/min rate was discontinued after 1 month because no weight loss was detected. It was replaced with an intermediate flow rate of 260 mL/min. It was assumed that the 900 mL/min flow rate was too fast, and that the effluent gas was not saturated with topiramate vapor. Three nitrogen flow rates were continued for the next several months, 120, 260 and 400 mL/min. The temperature ranged from 21.5°C to 25.0°C during the determination. The sample tubes were removed for weighing and calculation of the vapor pressure at monthly intervals. The determination required 5 months for completion.

## RESULTS

The data were evaluated by plotting the calculated vapor pressure vs. the cumulative volume of gas at each time point. Plots were constructed for each compound using the data from a single flow rate of nitrogen and by combining the data from multiple flow rates. Plots of the vapor pressure vs. total volume for each of the four flow rates used in the naphthalene determinations are presented in Figures 4-7. When the data for the four flow rates were combined (Figure 8), it was easier to interpret and analyze. Three phases were observed. The initial pre-equilibrium phase is characterized as a rate of decline with scatter in the calculated vapor pressures. This was followed by an equilibrium phase characterized by successive calculated vapor pressures that were approximately the same or fell within a narrow range and were in the flat, horizontal portion of the figure. The vapor pressure values reported for each compound were obtained from by calculating the mean for those values in the second flat, horizontal phase. The third phase was characterized by a rate of decline in vapor pressures. This decline indicated that there was insufficient sample remaining in the tube. The third phase was only observed with naphthalene, but could have been observed with topiramate and benzoic acid if the duration of testing and total flow of nitrogen had been extended.

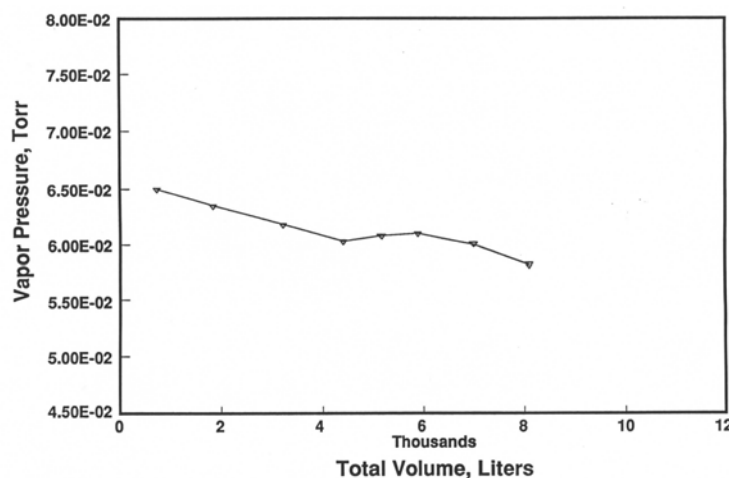


Figure 4. Vapor Pressure of Naphthalene at 22.2°C to 23.5°C as a Function of Total Gas Volume, 260 mL/min.

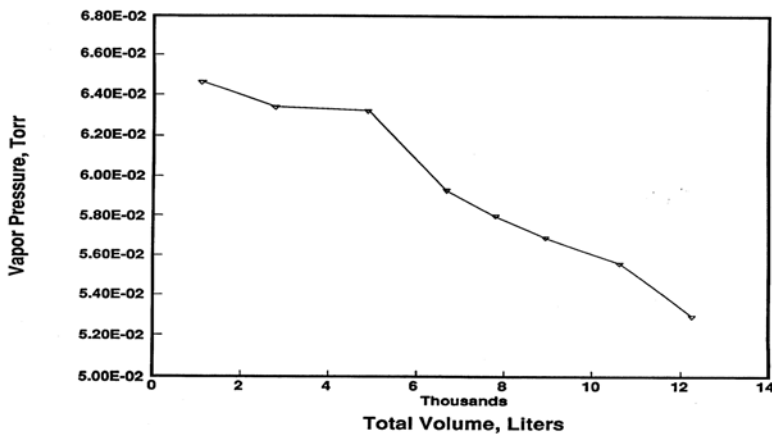


Figure 5. Vapor Pressure of Naphthalene at 22.2°C to 23.5°C as a Function of Total Gas Volume, 400 mL/min Flow Rate.

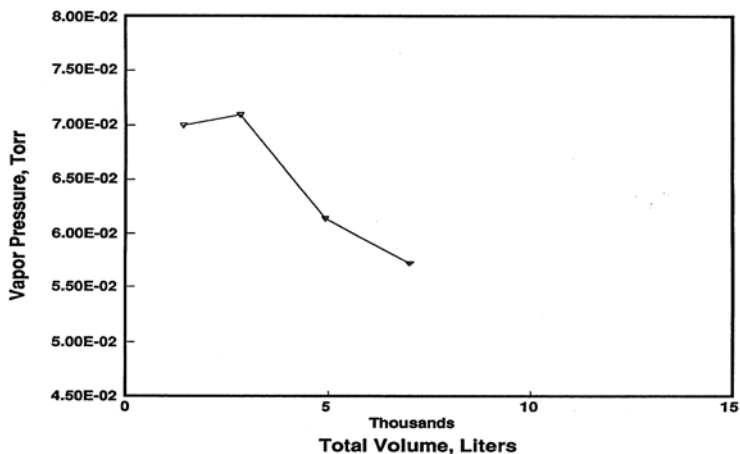


Figure 6. Vapor Pressure of Naphthalene at 22.2°C to 23.5°C as a Function of Total Gas Volume, 500 mL/min Flow Rate.

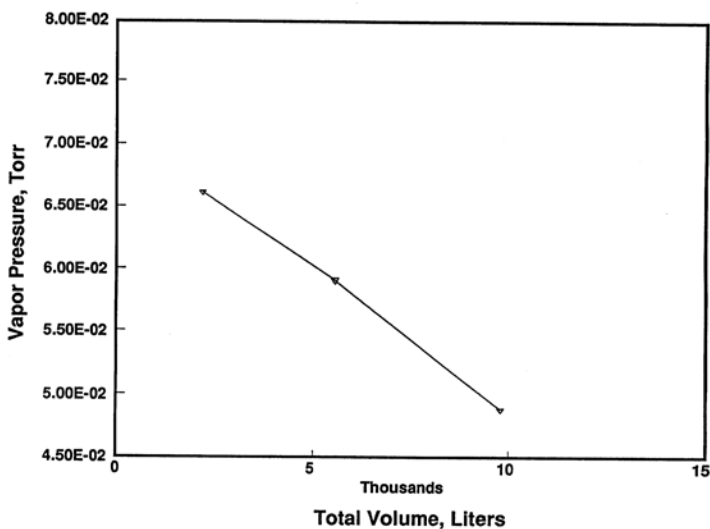


Figure 7: Vapor Pressure of Naphthalene at 22.2°C to 23.5°C as a Function of Total Gas Volume, 800 mL/min Flow Rate.

The scatter in the initial pre-equilibrium phase is attributed to insufficient volume of cumulative flow and insufficient saturation for equilibrium. The scatter is most noticeable with the slowest flow rates. This is most evident in comparing Figures 9 and 10, in which Figure 10 contains only three flow rates and Figure 9 contains five flow rates. By omitting the slowest rate, 32 mL/min, most of the scatter disappears from Figure 5. Equilibrium is reached when the ratio of the mass evaporated ( $m$ ) divided by the cumulative volume ( $V$ ) is constant or nearly constant. In the third phase the ratio of  $m/V$  decreases over time and the values of the vapor pressure ( $P$ ) experience a downward trend.

## NAPHTHALENE

Figures 4 to 7 which represent the experimental data for naphthalene at a single flow rate demonstrate the difficulty of analyzing the data. The data for four flow rates are combined in Figure 8, i.e., 260, 400, 500, and 800 mL/min. Combining the data made it easier to identify the equilibrium phase. The vapor pressure was calculated from the mean of the values in Figure 8 where the calculated vapor pressures are ca.  $6 \times 10^{-2}$  Torr and the total volume is between 3,000 and 7,000 L. The experimental mean vapor pressure value of  $6.07 \times 10^{-2}$  Torr (standard deviation is  $5.03 \times 10^{-3}$  Torr) obtained at 22.2°C to 23.5°C is in close agreement with the calculated  $6.28 \times 10^{-2}$  Torr and experimental  $8.21 \times 10^{-2}$  Torr values at 25°C reported by Wiedemann (2).

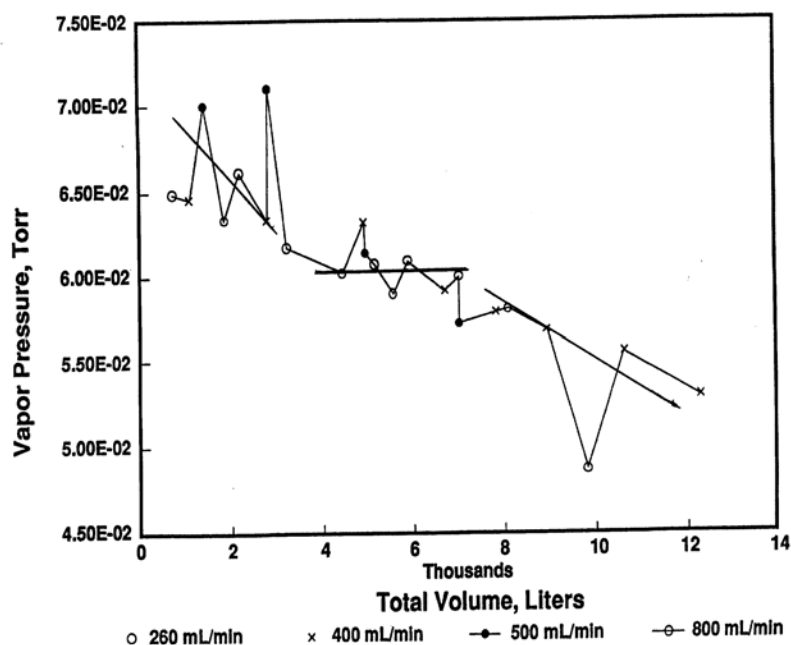
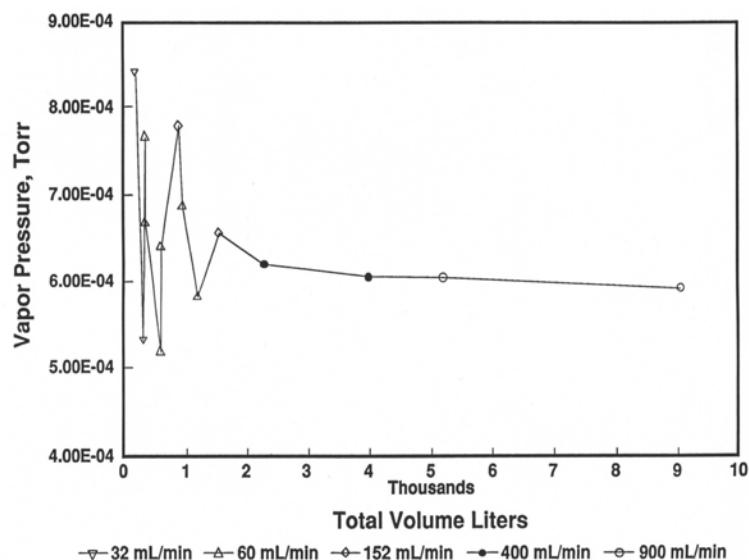


Figure 8. Vapor Pressure of Naphthalene at 22.2°C to 23.5°C as a Function of Total Gas Volume, 260, 400, 500, and 800 mL/min Flow Rates.

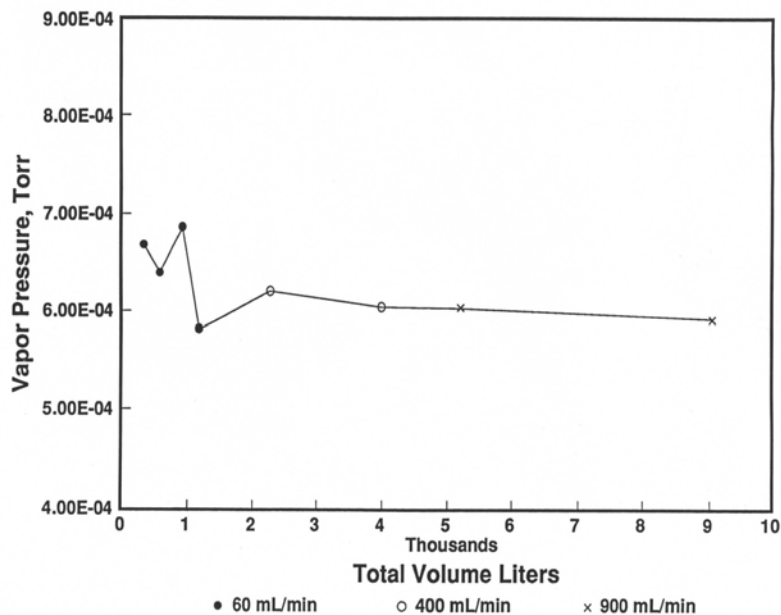
## BENZOIC ACID

Figure 9 was constructed using all of the vapor pressure data obtained using 32, 60, 152, 400 and 900 mL/min flow rates. The total volumes of nitrogen gas were between 180 and 9,051 L. Figure 10 was constructed using fewer flow rates. Comparison of Figures 9 and 10 demonstrates that “slow” flow rates, 32, 60 and 152 mL/min with less than 1 L of flow provided insufficient total flow volumes and only add to the scatter. Both figures show that the calculated vapor pressure approaches a flat, horizontal range as the total volume increases. The third post-equilibrium phase was not observed. However there were sufficient data to establish the equilibrium phase and calculate a mean vapor pressure.



**Figure 9. Vapor Pressure of Benzoic Acid at 22.0°C to 24.4°C as a Function of Total Gas Volume 32, 60, 150, 400 and 900 mL/min Flow Rates.**

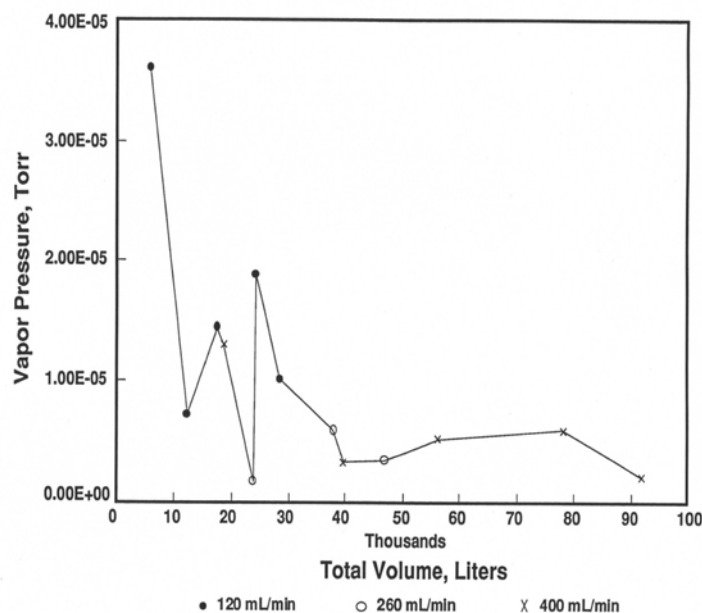
The six experimental vapor pressure values in Figure 10 which are similar in magnitude, range between  $5.81$  and  $6.56 \times 10^{-4}$  Torr, in the almost horizontal portion of the plot were used to calculate the mean vapor pressure of benzoic acid,  $6.09 \times 10^{-4}$  Torr (standard deviation is  $2.65 \times 10^{-5}$  Torr). This is in close agreement with the vapor pressure of benzoic acid  $8.86 \times 10^{-4}$  Torr at  $21.4^\circ\text{C}$  reported by Wiedemann (2). The agreement of the experimental values for the reference compounds with the literature values validated the apparatus and validated the methods used for calculation of the vapor pressures.



**Figure 10. Vapor Pressure of Benzoic Acid at 22.0°C to 24.4°C as a Function of Total Gas Volume, 60, 400 and 900 mL/min Flow Rates.**

## TOPIRAMATE

The topiramate determination was similar to the benzoic acid determination in that only the pre-equilibrium and equilibrium phases are observed; however, there are sufficient data in the observed equilibrium phase to calculate a mean vapor pressure. The combined results for the 120, 260 and 400 mL/min flow rates are presented in Figure 11. The equilibrium phase is where the experimental vapor pressure values reach a flat value between  $1 \times 10^{-6}$  and  $6 \times 10^{-6}$  Torr after the total volume of gas exceeds 20,000 to 30,000 L. A mean vapor pressure of  $3.84 \times 10^{-6}$  Torr was calculated from the seven experimental values obtained within this range. The standard deviation is  $1.77 \times 10^{-6}$  Torr. None of the vapor pressures obtained at the 120 mL/min flow rate reached the  $1 \times 10^{-6}$  to  $6 \times 10^{-6}$  Torr equilibrium phase.



**Figure 11. Vapor Pressure of Topiramate at 21.5°C to 25.0°C as a Function of Total Gas Volume, 120, 260 and 400 mL/min Flow Rates.**

## ACKNOWLEDGEMENTS

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