A Thermogravimetric Analysis of Non-polymeric Pharmaceutical Plasticizers: Kinetic Analysis, Method Validation, and Thermal Stability Evaluation

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ABSTRACT

Four non-polymeric plasticizers, propylene glycol, diethyl phthalate, triacetin, and glycerin have been subjected to rising temperature thermogravimetry for kinetic analysis and vaporization-based thermal stability evaluation. Since volatile loss of a substance is a function of its vapor pressure, the thermal stability of these plasticizers has been analyzed by generating vapor pressure curves using the Antoine and Langmuir equations. Unknown Antoine constants for the sample compounds, triacetin and glycerin have been derived by subjecting the vapor pressure curves to nonlinear regression. For the first time, the entire process of obtaining the unknown Antoine constants through thermogravimetry has been validated by developing an approach called the 'double reference method.' Based on this method, it has been possible to show that this technique is accurate even for structurally diverse compounds. Kinetic analysis on the volatilization of compounds revealed a predominant zero order process. The activation energy values for vaporization of propylene glycol, diethyl phthalate, triacetin, and glycerin, as deduced from the Arrhenius plots, have been determined to be 55.80, 66.45, 65.12, and 67.54 kJ/mol, respectively. The enthalpies of vaporization of the compounds have been determined from the Clausius-Clapeyron plots. Rising temperature thermogravimetry coupled with nonlinear regression analysis has been shown to be an effective and rapid technique for accurately predicting the vapor pressure behavior and thermal stability evaluation of volatile compounds.

KEYWORDS: plasticizers, vapor pressure plots, thermal stability, Antoine and Langmuir equations, thermogravimetry

INTRODUCTION

Plasticizers are widely employed in the pharmaceutical industry for applications such as coating aids in functional and nonfunctional coating of solid dosage forms, including tablets, beads, and granules, and in the production of soft gelatin capsules. In the process, plasticizers are subjected to elevated thermal conditions that could lead to physical destabilization through vaporization, thereby leading to undesirable effects. Low-molecular-weight plasticizers are generally volatile and tend to evaporate in their free state or from a plasticized product upon exposure to elevated thermal conditions. Evaporation from polymers into the surrounding air is the most common form of plasticizer loss. For plasticizers with low boiling points, evaporation occurs continuously, even at low temperatures, although it may be undetectable even by sensitive analytical techniques.¹ Because of plasticizer loss, the plasticized product will lose its flexibility and distensibility to an extent that may be technically significant and hinder the plasticizer's use in the application intended. Working with a non-polymeric plasticizer, triethyl citrate, for film coating of pellets and tablets, Thoma and Bechtold² observed a loss of up to 65% plasticizer due to volatilization at elevated temperatures. Hence, thermal characterization with stability assessment is a very important factor in the choice of a plasticizer. Since a plasticizer will interact differently with different polymers, its stability from the plasticized product has to be assessed individually. However, literature¹ suggests that the vapor pressure values of free plasticizers are representative of their volatility from the plasticized product.

In the current study, non-polymeric plasticizers used widely in the pharmaceutical industry have been analyzed in their free form using rising temperature thermogravimetry. The volatile loss of a compound at any temperature point is directly proportional to its vapor pressure. Hence, development of a rapid method for construction of vapor pressure plots would greatly help in assessing a plasticizer's thermal stability over a given temperature range. Several methods of vapor pressure determination, such as direct measurement using a manometer,³ measurement of sample volatilization by vacuum effusion,⁴ and boiling point determination under controlled pressure,⁵ have been previously used. Isothermal thermogravimetry was used as early as 1973 for determination of rates of volatilization of pesticides at

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ambient pressure.⁶ Rising temperature thermogravimetry is a relatively simple technique by which vapor pressure plots can be constructed using Langmuir and Antoine equations. Most of the pharmaceutically important non-polymeric plasticizers in their free form exhibit a zero order evaporation process when subjected to controlled temperature programs. A true zero order process can be readily distinguished by the characteristic sharp fall on the differential thermogravimetric (DTG) curve. Vapor pressure plots for such compounds exhibiting a zero order evaporation process can be constructed using thermogravimetry. Price and Hawkins used rising temperature thermogravimetry for construction of vapor pressure plots for two disperse dyes using the Langmuir equation.

Kinetic analysis

The kinetic reaction mechanism for volatilization of compounds can be determined from the Arrhenius equation,

$$K = Ae^{-\frac{E_a}{RT}} \quad (1)$$

where E_a is the activation energy of evaporation; R is the universal gas constant; A is the pre-exponential factor; T is the absolute temperature; and K is the reaction rate constant, which can be determined as explained in a previous study.⁸

The above equation upon log transformation can be rewritten as

$$\ln K = \ln A - \frac{E_a}{RT} \quad (2)$$

The activation energy can be determined from the slope of the above plot, and the intercept value would yield the pre-exponential factor.

Antoine and Langmuir equations

The vapor pressure of a substance is directly proportional to the temperature of the system. The temperature dependence of vapor pressure for a substance has been expressed using different mathematical equations, two such equations being the Antoine and the Langmuir equations.⁷ Over a moderate pressure range, the Antoine equation for vapor pressure determination can be written as

$$\ln P = a - \frac{b}{T+c} \quad (3)$$

where P is the vapor pressure of the substance under investigation; T is the absolute temperature in Kelvin; and a is 2.303A, b is 2.303B, and c is 2.303C. Here A, B, and C are Antoine constants; hence, Equation 3 can be rewritten as

$$\log P = A - \frac{B}{T+C} \quad (4)$$

The Antoine constants are defined for specific temperature ranges, and the vapor pressure values obtained are valid over those temperature ranges only. Therefore, application of these constant values outside these ranges will lead to incorrect estimation of vapor pressure values.

The rate of volatile mass loss of a substance is related to its vapor pressure and can be expressed with the help of the Langmuir equation given below:

$$P = \left[\frac{\sqrt{2\pi R}}{\alpha} \right] * \left[\frac{dm}{dt} \sqrt{\frac{T}{M}} \right] \quad (5)$$

where P is the vapor pressure, R is the universal gas constant, α is the vaporization coefficient (taken as unity in vacuum), dm/dt is the rate of volatile mass loss with respect to time, T is the absolute temperature, and M is the molecular weight of the substance in the vapor phase. The Langmuir equation can be rewritten as shown in Equation 6, wherein the vapor pressure values can be expressed as a product of two components, k_{evap} and v . k_{evap} is the coefficient of evaporation and is a constant for a set of experimental conditions, as explained in the following section. v is the factor dependent on the compound being analyzed and can be determined from a thermogravimetric experiment.

$$P = k_{\text{evap}}(v) \quad (6)$$

This equation had been derived by Langmuir⁹ when working in vacuum conditions, and in this case the value of the vaporization coefficient (α) has been taken as unity. During thermogravimetric studies, if the sample is purged under a constant flow rate of a purge gas, then the value of α can no longer be taken as unity. Hence, a modification of the Langmuir equation is imperative in non-vacuum conditions. However, this problem can be overcome by determining the k_{evap} value by calibration with substances of known vapor pressure.

The enthalpy of vaporization is a characteristic parameter of a substance that reflects the amount of heat energy required to vaporize one mole of the substance. The Clausius-Clapeyron equation given below has been extensively used¹⁰ to study the dependency of vapor pressure of liquids over temperature.

$$\ln P = -\frac{\Delta H}{R} \left[\frac{1}{T} \right] + c \quad (7)$$

This equation over a given temperature range {T1, T2} can be used to determine the enthalpy of vaporization (ΔH_{vap}) of substances if the vapor pressure values over the temperature range are known.

Construction of vapor pressure plots

The Antoine and Langmuir equations can be employed together not only for rapid construction of the vapor pressure curves but also for determination of unknown Antoine constants for sample compounds. A more detailed report on the methodology used can be found in a recent work.¹¹ The current work involves examining the technique in greater detail, analyzing certain aspects of the use of this methodology that can have significant implications on the results and data interpretation, developing a method for proper validation of the entire technique and analysis of four pharmaceutically important plasticizers for kinetic and stability evaluation. The use of reference compounds in construction of the vapor pressure plots for the sample compounds utilizes the concept of substance-independence of the coefficient of evaporation, k_{evap} . The coefficient of evaporation is a measure of the evaporation process that depends on parameters such as the area of the surface from which evaporation is taking place, the vaporization coefficient, and the universal gas constant but does not depend on the material being investigated. Thus, it is a substance-independent parameter that is universal for all substances undergoing a true zero order evaporation process. In the present study, rising temperature thermogravimetry has been employed for a thermal analysis study of four non-polymeric plasticizers: propylene glycol, diethyl phthalate, triacetin, and glycerin. The Antoine constants for propylene glycol have been reported in the literature,¹² and hence its vapor pressure plot can be constructed directly using the Antoine equation given above. In the current work all units have been reported in the SI system, thus pressure units have been reported in pascals. The Antoine constants may differ based upon the units used for pressure, as explained in the Results and Discussion section. Hence, for comparison purposes, it is deemed best to maintain the same units. The Antoine constants for a compound are specific for a given temperature range. Hence, vapor pressure values outside the range can be calculated only from a separate set of Antoine constants defined for that temperature range. For compounds whose Antoine constants are not reported in the literature, vapor pressure plots can be constructed and unknown Antoine constants determined by the combined use of the Antoine and Langmuir equations.

The activation energies (E_a) in kJ/mol and the pre-exponential factors ($\ln A$) have been deduced from the Arrhenius plots. Vapor pressure plots for all four plasticizers have been constructed, and the unknown Antoine constants for the sample compounds triacetin and glycerin have been derived using nonlinear regression analysis. Verification of the Antoine constants thus ob-

tained is highly imperative to judge the accuracy of the thermogravimetric analysis and the nonlinear regression analysis, which have been employed together to obtain the unknown Antoine constants. A major objective of this study was to develop a simple methodology for validating the entire procedure. For this purpose, the 'double reference method' has been developed, which, as discussed in the Results and Discussion section, effectively validates the entire procedure and the unknown Antoine constants. The latent heats of vaporization of the four compounds have been determined from the Clausius-Clapeyron plots.

MATERIALS AND METHODS

Materials

Laboratory-grade propylene glycol, $\geq 99.5\%$ pure (Lot 700841), was obtained from Fischer Scientific, Pittsburgh, PA; diethyl phthalate, 99.5% pure (Lot 8A), from Eastman Organic Chemicals, Kingsport, TN; triacetin, $>99\%$ pure (Lot 7234), from Ruger Chemical Company, Irvington, NJ; and glycerin, 99+% pure, from Colgate Palmolive, Morristown, NJ. All plasticizers were analyzed as received. A simultaneous thermogravimetry-differential thermal analysis (TG-DTA) unit, SDT 2960, TA Instruments, New castle, Delaware was used for the thermogravimetric studies.

Methods

Thermogravimetric experiments were carried out on the reference compound, propylene glycol, under varying temperature gradients (2, 5, 10, and 15°C/min) and purge gas flow rates (75, 100, and 125 mL/min). All other plasticizers were subjected to a controlled temperature program, which involved heating the samples from ambient temperature to 400°C at a rate of 2°C per minute under a purge gas flow rate of 100 mL/min.^{Endnote}

¹ All experiments were carried out in 110- μL platinum crucibles with a cross-section area of 0.3399 cm², and the samples were purged with dry nitrogen at a constant flow rate. The use of the purge gas, dry nitrogen was essential in order to avoid oxidation of the plasticizers, which would be made possible by purge gases such as pure oxygen or air. Reaction kinetics were evaluated using Arrhenius plots. Vapor pressure plots were constructed for sample and reference compounds using a combination of Antoine and Langmuir equations. Unknown Antoine constants were deduced by nonlinear regression using SPSS version 10.0 (SPSS Inc., Chicago, Illinois). Comparative thermal stability evaluation, to rank the compounds, was done based on the rates of volatilization values (dm/dt) deduced from the Antoine constants. The heats of vaporization of the plasticizers were determined from the slopes of the $\ln P$ versus $1/T$ plots in accordance with the Clausius-Clapeyron equation.

Figure 1. A TG-DTG plot of propylene glycol at a heating rate of 2°C/min and a purge gas flow rate of 100 mL/min.

Table 1. Activation Energy Values (Obtained From Arrhenius Plots) in kJ/mol for Propylene Glycol at Varying Temperature Gradients and Purge Gas Flow Rates

Ramp	Flow Rate		
	75 mL/min	100 mL/min	125 mL/min
2°C/min	54.01	55.80	55.87
5°C/min	54.89	55.08	52.77
10°C/min	56.05	54.58	58.37
15°C/min	55.73	56.53	51.28

RESULTS AND DISCUSSION

Kinetic analysis

The thermograms of all four plasticizers exhibited a typical zero order evaporation process, as observed from the characteristic sharp linear fall of the DTG curves. A representative TG/DTG plot for propylene glycol at a heating rate of 2°C/min and a purge gas flow rate of 100 mL/min has been shown **Figure 1**. The thermogravimetric curve indicates a complete evaporation process, with the entire sample evaporating from the constant reaction interface in the crucibles. The kinetic mechanism of the reactions was verified by plotting an Arrhenius plot ($\ln K$ vs. $1/T$), wherein a straight line indicates a zero order

reaction. The plots thus obtained exhibited high linearity, reconfirming a zero order process. The effect of varying experimental conditions such as temperature gradients and purge gas flow rates on the activation energy value of propylene glycol has been studied. In all cases the kinetic mechanism was confirmed to be zero order.¹³ The activation energy values under these varying conditions have been presented in **Table 1**. The kinetic mechanisms for diethyl phthalate, triacetin, and glycerin have also been confirmed to be zero order from the Arrhenius plots (**Figure 2**), and the activation energy values have been determined to be 66.45, 65.12, and 67.54 kJ/mol, respectively, from thermogravimetric experiments conducted at a temperature gradient of 2°C/min and a flow rate of 100 mL/min. Thus, it can be said that

Figure 2. Determination of kinetic mechanism for volatilization of triacetin, diethyl phthalate, and glycerin from Arrhenius plots.

Figure 3. Vapor pressure plots for the reference compounds propylene glycol (PG) and diethyl phthalate (DEP) (Antoine/Langmuir, and derived fits, resolved in inset).

the rate of volatilization of these non-polymeric plasticizers in their free form is independent of the amount of plasticizer present in the liquid phase.

Construction of vapor pressure plots

The vapor pressure plot for propylene glycol has been constructed directly based on the Antoine equation (**Figure 3**), as its Antoine constants are reported in the literature. A thermogravimetric experiment was conducted on the reference compound propylene glycol,

Figure 4. k_{evap} determination from the reference compound propylene glycol from the slope of a plot of pressure versus v .

Figure 5. Vapor pressure plots for the sample compounds glycerin and triacetin (Langmuir and derived fits, resolved in inset).

and the coefficient of evaporation (k_{evap}) value was obtained from the slope of the plot between pressure and v (**Figure 4**). The k_{evap} value was found to be $148246.8 \text{ Pa}^1 \text{ kg}^{-0.5} \text{ m}^{-2} \text{ sec}^{-1} \text{ K}^{-0.5}$ by calibration with the reference compound. Since this component is substance independent, this value was substituted into the Langmuir

equation along with the v values obtained from the thermogravimetric experiments, for determining the vapor pressure values at different temperature points for diethyl phthalate^{Endnote 2}, triacetin, and glycerin and thus constructing their vapor pressure plots (**Figures 3** and **5**). A fundamental and important rule in evaporation studies is that vaporization analysis can be done on only

Figure 6. A TG-DTG plot of diethyl phthalate at a heating rate of 2°C/min and a purge gas flow rate of 100 mL/min.

the rising temperature portion of the DTG curve. This is the region where essentially all evaporation takes place. Before this temperature range, the sample has not started evaporating, and after this range, the sample has completely evaporated, as can be seen from the zero sample weight on the thermogravimetric curve. For example, in the case of propylene glycol, we can see from **Figure 1** that the rising temperature portion of the DTG curve ranges from about 350 to 410 K (Instrument output in °C has been converted to Kelvin). Hence, though the Antoine constants for this compound are reported over a temperature range of 318 to 461 K, vaporization analysis can be done from only 350 to 410 K. Similarly, in the case of diethyl phthalate, the rising temperature portion extends from about 410 to 460 K (**Figure 6**), and hence the analysis has been done over that range.

When vapor pressure plots are constructed using the Antoine and Langmuir equations, it has to be noted that the coefficient of evaporation term (k_{evap}) is independent of substance but not independent of temperature. The k_{evap} value, which is derived from the slope of pressure versus v , can be affected by change in temperature in the following ways:

1. Since Antoine constants are defined for a given temperature range, if the temperature range of analysis for the sample compound is outside the range over which the reference Antoine constants are defined $\{T1, T2\}$, then the k_{evap} derived using these Antoine constants could be erroneous, be-

cause outside the range $\{T1, T2\}$ the Antoine constants could change significantly, thus changing the pressure and in turn altering the k_{evap} value (explained below).

2. Since v is a function of temperature, its variation with temperature can also lead to a change in k_{evap} . However, as explained below, in the current study it was observed that the variation in k_{evap} due to the variation in v is minimal as long as the reference Antoine constants are valid over the range of analysis.

A recent work¹¹ that used thermogravimetry for calculation of vapor pressure plots and determination of unknown Antoine constants used the Antoine constants for the reference compounds over a certain temperature range $\{T1, T2\}$ to evaluate k_{evap} . This k_{evap} value was then used to derive the unknown constants of a sample compound over a temperature range that was outside the range $\{T1, T2\}$. When doing so, significant errors in the estimation of unknown Antoine constants can result, as the k_{evap} value is derived from the slope of the plot between the vapor pressure values obtained from the Antoine equation and the v value obtained from the thermogravimetric experiment. Since the Antoine constants are defined for only a given temperature range, the k_{evap} obtained from the above-mentioned procedure can be applied only within this range. Though the coefficient of evaporation (k_{evap}) is a numerical value of the order of 10^{-5} , a change in the temperature range can

significantly affect the Antoine constants and hence the k_{evap} value, as seen in the case of diethyl phthalate, where the value of the constant C is -115.9 for 345 to 453 K, and 209.45 for 421 to 570 K. This reasoning can be further exemplified by the following calculations.

The Antoine constants for diethyl phthalate as reported in the literature¹² are as follows: A = 6.043, B = 1866.05, and C = -115.9 for the range 345 to 453 K; and A = 10.6902, B = 6768.3, and C = 209.45 for the range 421 to 570 K.

We have $P = 10^{(A - B/(T + C))}$ and $k_{\text{evap}} = Pv$,

The k_{evap} value at, say, 413 K, a temperature point where we have an experimentally determined v value and that lies in the first range 345 to 453 K and is outside the range 421 to 570 K can be calculated as follows

Calculated pressure using the correct set of constants:

$\log P = 6.043 - 1866.05/(413 - 115.9)$, $P = 0.57825$ kPa = 578.25 Pa

v as experimentally determined from a thermogravimetric run is $0.003763 \text{ kg}^{0.5} \text{ m}^{-2} \text{ sec}^{-1} \text{ K}^{0.5}$.

$k_{\text{evap}} = P/v = 578.25/0.003763 = 153686.8 \text{ Pa}^1 \text{ kg}^{-0.5} \text{ m}^2 \text{ sec}^{-1} \text{ K}^{-0.5}$

Calculated pressure from the constants defined over 421 to 570 K:

$\log P = 10.6902 - 6768.3/(413 + 209.45)$, $P = 0.65547$ kPa = 655.47 Pa

$k_{\text{evap}} = P/v = 655.47/0.003763 = 174210.4 \text{ Pa}^1 \text{ kg}^{-0.5} \text{ m}^2 \text{ sec}^{-1} \text{ K}^{-0.5}$

From this, we can understand that if we were even slightly outside the range 421 to 570 K, as in the above case, but were still using the constants defined for that range, the variation in k_{evap} would be large. In other words, since vapor pressure plots for sample compounds are constructed based on these k_{evap} values, they can be plotted only in the temperature range for which the Antoine constants for the reference compound have been defined. One reference compound used in the current work, propylene glycol, has Antoine constants A = 7.9118, B = 2554.9, and C = -28.611 reported for a temperature range 318 to 461 K.¹² Hence, in the current work, vapor pressure plots for sample compounds have been constructed in that temperature range only. The Antoine constants for the second reference compound, diethyl phthalate, have been reported as A = 6.043, B = 1866.05, and C = -115.9 for a temperature range 345 to 453 K. Since the temperature range over which diethyl phthalate constants are defined is a subset of the temperature range over which the primary reference, propylene glycol's, constants are defined, these

two compounds can be safely used for the entire validation section discussed below.

It should be mentioned that the Antoine constants for propylene glycol are defined over the temperature range 318 to 461 K and the entire analysis is restricted to this range. However, the thermogravimetric analysis on propylene glycol extends from 350 to 410 K and the analysis on diethyl phthalate extends from 410 to 460 K. This difference in temperature ranges could also possibly affect the k_{evap} value, because the v value, which is used to derive the k_{evap} value, is clearly a function of temperature. However, as indicated above, the k_{evap} value is a numerical value of the order of 10^5 , and from the analysis of propylene glycol it was observed that with the Antoine constants being the same, the % coefficient of variation (% CV) in k_{evap} due to a variation in v with temperature over a 60 K range is as low as 1.29%. On the other hand, the wide variation in Antoine constants with temperature could affect the k_{evap} value to a greater extent than the variation in v with temperature. The variation in v , as indicated above, is minimal as long as the primary reference's Antoine constants remain the same over the entire region of analysis. The variation in v with temperature may not necessarily be as low if the temperature range of analysis is too large. Hence, the variation in k_{evap} as a result of variation in v over the temperature range of interest must be determined before extending this analysis. The point that k_{evap} was minimally affected by change in v with change in temperature is further supported by the fact that the validation of the results using the above two compounds (explained in the following section) resulted in derived pressure values that were in excellent agreement with values cited in literature.^{12,14}

From the Clausius-Clapeyron plot for propylene glycol (**Figure 7**), an enthalpy of vaporization value of 57.00 kJ/mol was obtained, which is in good agreement with that reported in the literature.¹⁴ The enthalpy of vaporization values for diethyl phthalate, triacetin, and glycerin determined in a similar fashion were found to be 68.26, 66.89, and 67.89 kJ/mol, respectively. The unknown Antoine constants for the sample compounds triacetin and glycerin as determined from the above-mentioned technique were A = 7.0190, B = 678.8597, and C = -237.1748; and A = 9.049, B = 1630.6957, and C = -156.6293, respectively.

Method validation-double reference method

Since the vapor pressure curves of diethyl phthalate, triacetin, and glycerin were subjected to nonlinear regression using the statistical package SPSS 10.0 for the determination of the unknown Antoine constants, validation of the entire process is imperative. For the first time, the current work has demonstrated the accuracy with which thermogravimetry can be employed for the

Figure 7. Determination of enthalpy of vaporization for polyethylene glycol (PG), diethyl phthalate (DEP), triacetin, and glycerin from Clausius-Clapeyron plots.

determination of unknown Antoine constants. First, the statistical analysis of the curve through nonlinear regression was verified on the reference compound. The Antoine constants derived through the nonlinear regression analysis of vapor pressure plots of propylene glycol ($A = 7.912$, $B = 2554.899$, $C = -28.611$) were in very good agreement with the reported literature values ($A = 7.911$, $B = 2554.9$, and $C = -28.611$) and the reported and derived curves completely overlapped, as shown in **Figure 3**, thus verifying the nonlinear regression process. Although this process verifies the statistical analysis, the entire process of constructing the vapor pressure plots by thermogravimetry using the Langmuir and Antoine equations still needs to be verified in order to validate the constants thus obtained by an indirect procedure. For this, the double reference method has been developed.

Two compounds, diethyl phthalate and propylene glycol, were chosen because both have Antoine constants reported in the literature. Propylene glycol had Antoine constants reported over a temperature range of 318 to 461 K, and diethyl phthalate had Antoine constants reported over a temperature range of 345 to 453 K (refer to 'Construction of vapor pressure plots' section for values). Propylene glycol was used as a reference, and diethyl phthalate was used as a pseudo-sample (since the Antoine constants are known for this compound). A thermogravimetric run was conducted on propylene glycol to determine the substance-dependent component v

of the Langmuir equation. Since the Antoine constants for propylene glycol are reported, vapor pressure values for a range of temperature points coinciding with the rising portion of the DTG curve could be determined. Since we had both the pressure and the v values, we could find the substance-independent component (k_{evap}) of the Langmuir equation. This value was determined to be $148246.8 \text{ Pa}^1 \text{kg}^{-0.5} \text{m}^2 \text{sec}^1 \text{K}^{-0.5}$ for the experimental parameters specified in the Methods section. A thermogravimetric run on the pseudo-sample, namely diethyl phthalate, was conducted, and the substance-dependent component v was determined. Using the k_{evap} obtained from propylene glycol and the v value obtained from the thermogravimetric experiment on diethyl phthalate, the vapor pressure values for diethyl phthalate could be determined and the vapor pressure plots constructed. When subjected to nonlinear regression analysis based on the Antoine equation, these plots would give the Antoine constants. If the entire process holds true, the Antoine constants thus obtained should be in close agreement with the Antoine constants reported in the literature. In the current study, the units for pressure were pascals (because SI units were used throughout) and the reported Antoine constants were based on the pressure units of kilopascals. Hence, pressures in common units, instead of Antoine constants, have been compared to validate the process. A more important reason for using pascals is that the starting block for iterations when doing the nonlinear regression analysis has been

Table 2. A Comparison Between Vapor Pressure Values Based on Derived and Reported (in the Literature) Antoine Constants for Diethyl Phthalate Using the Double Reference Method

Diethyl Phthalate	A	B	C	Pressure at 445 K $P = 10^{(A-B/(T+C))}$ Pascals
Derived Antoine constants (pressure units in Pa)	8.0151	1226.9477	-180.1647	2411.1
Reported Antoine constants (pressure units in kPa)	6.0431	1866.0500	-115.9000	2360.1

standardized by American society of testing and materials (ASTM) ¹⁵ as A = 9.3, B = 2000, and C = -37 when pressure units are in pascals. These are the initial values that were used in this study, and hence pressure has been expressed in pascals.

From **Table 2**, we can see that the experimentally determined pressure values are in excellent agreement with the pressure values reported in the literature, thus validating the entire process. Also, a significant outcome of this work is that it indicates that the compounds being analyzed need not be from the same chemical class, as has been indicated by Chatterjee et al.¹¹ In spite of the fact that propylene glycol, an aliphatic alcohol, and diethyl phthalate, an aromatic ester, belong to different chemical classes, the double reference method shows the accuracy with which these two dissimilar compounds can be used for rapid construction of vapor pressure plots and determination of unknown Antoine constants using rising temperature thermogravimetry. Hence, this entire procedure can be used with confidence as long as the temperature restrictions explained in the above section are followed, the convergence criterion in the nonlinear regression process is met, and the molecular weight of the compounds in the vapor phase is known. In the case of compounds existing as dimers and other association products in the vapor phase (e.g. compounds containing carboxylic acids), the corrected molecular weight of the dimer should be used rather than the molecular weight of a monomer molecule.^{9,16}

Comparative stability evaluation

The vapor pressure of a substance reflects its escaping tendency, and hence comparative stability evaluation between substances can be done based on the vapor pressure plots. However, we can infer from the Langmuir equation that the rate of volatilization of a substance is a function of not just its vapor pressure but also its molecular weight. Hence, it would be more appropriate to do comparative stability analysis based on the rates of

do comparative stability analysis based on the rates of volatilization (dm/dt) values. These can be determined from the vapor pressure values by a simple manipulation based on the Langmuir equation:

$$\frac{dm}{dt} = \frac{P}{k_{\text{evap}}} * \sqrt{\frac{M}{T}} \quad (8)$$

Since k_{evap} and molecular weight (M) are known constants, we can calculate the dm/dt value at any temperature if the vapor pressure value is known. Hence, if we know the Antoine constants of the substance under investigation, we can rapidly generate rates of volatilization plots and learn the substance's thermal stability without any experimentation. The k_{evap} can be found out from a single thermogravimetric experiment and will remain the same for all compounds under investigation when the same experimental conditions are maintained, because it is substance independent. Vapor pressure values vary with temperature, because they are a direct function of absolute temperature; hence, comparison of plasticizers' thermal stability should be done for a stated temperature point or a temperature range that extends for all the compounds under study. A sample common temperature range for comparing the thermal stability was identified as 443 to 448 K. **Table 3** provides a comparison of the vapor pressure and rates of volatilization values of diethyl phthalate, triacetin, and glycerin. This table helps in predicting the rank order of thermal stability of the three plasticizers based on their rates of volatilization, which in increasing order of stability are triacetin, diethyl phthalate, and glycerin. The vapor pressure plot for propylene glycol extended from 368 to 398 K. Since this does not coincide with the above-mentioned range, it was not grouped with the other plasticizers. However, the dm/dt value at 398 K for propylene glycol is 0.00092 kg/m²/sec, and hence over the region of comparison (443-448 K), it will have a higher dm/dt value. The highest dm/dt value in **Table 3** is 0.00093-for triacetin at 448.00 K. Hence it can be concluded that

Table 3. Comparison of the Plasticizer Vapor Pressure and Rates of Volatilization Values for a Given Temperature Range

Comparative Thermal Stability Vapor Pressure (VP, Pa) and Rates of Volatilization (dm/dt, kg/m ² /sec)						
Temperature (K)	Glycerin		Diethyl Phthalate		Triacetin	
	VP	dm/dt	VP	dm/dt	VP	dm/dt
443	2265.7	0.00022	2227.0	0.00033	5269.9	0.00078
444	2367.2	0.00023	2326.6	0.00034	5456.2	0.00081
445	2477.0	0.00024	2419.7	0.00036	5642.8	0.00084
446	2589.5	0.00025	2512.6	0.00037	5823.4	0.00087
447	2705.9	0.00026	2621.0	0.00039	5987.8	0.00090
448	2835.1	0.00027	2721.9	0.00040	6146.0	0.00093

propylene glycol will be less stable than the other 3 plasticizers. This data would be very useful when plasticizers are chosen from the viewpoint of thermal stability.

CONCLUSION

Four non-polymeric pharmaceutical plasticizers analyzed using thermogravimetry exhibited zero order kinetic mechanism for volatilization. Rising temperature thermogravimetry has been shown to be an effective and reliable technique for construction of vapor pressure plots based on Antoine and Langmuir equations. Using the double reference method as a validation tool, it has been demonstrated that thermogravimetry in combination with nonlinear regression can be employed for an accurate determination of unknown Antoine constants for sample compounds, even in cases where the reference and sample compounds are from different chemical classes. In the absence of Antoine constants, a thermogravimetric experiment would enable rapid construction of vapor pressure plots; and in the presence of Antoine constants, vapor pressure plots can be constructed without the need for any experimental procedures, provided the details as described in the Results and Discussion section are kept in mind. This would provide for a rapid means for thermal characterization of not only plasticizers but also all other thermo-labile substances used for various pharmaceutical applications and could

possibly be used as a method for accelerated stability analysis of plasticized products.

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ENDNOTES

¹ All temperature values are accurate to 0.01°C.

² Antoine constants for DEP are available in literature. Hence it was used as a secondary reference in the validation section.

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