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Research paper

Estimating vapor pressure curves by thermogravimetry: a rapid and convenient method for characterization of pharmaceuticals

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Abstract

The purpose of this study was to investigate a rapid method for the evaluation of vaporization characteristics for selected benzoic acid derivatives. The compounds studied in this context were the *ortho*-, *meta*- and *para*-derivatives of hydroxy and amino benzoic acids. Calculations for the order of reaction were first carried out for each of the compounds using methyl paraben as the calibration standard. Those compounds undergoing zero order, non-activated evaporation processes, were analyzed by the Antoine and Langmuir equations, conjointly. The coefficient of vaporization was obtained as $1.2 \times 10^5 \pm 0.8$ Pa kg$^{0.5}$ mol$^{0.5}$ s^{-1}m^{-2} K$^{-0.5}$. The vapor pressure values were used to determine the Antoine constants using the SPSS 10.0 software. This study attempts to outline a comprehensive thermogravimetric technique for vapor pressure characterization of single-component systems. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Vapor pressure; Antoine equation; Langmuir equation; Benzoic acid derivatives; Thermogravimetry; Pharmaceutical characterization

1. Introduction

There have been several attempts to date to devise and validate methods for vapor pressure measurements. These involve direct measurements with a manometer [1], the use of mass spectrometry to monitor the gas phase concentration of the volatile species [2], the measure of sample volatilization by vacuum diffusion in a Knudsen cell [3] and the boiling point determination under reduced pressures [4].

The use of thermogravimetry to study vaporization was probably first demonstrated by Gueckel et al. [5], where they measured the volatilization rates of pesticides at ambient pressures by isothermal thermogravimetry. The main principle governing the experiment is that evaporation and sublimation are zero-order processes; hence the rate of mass loss of a compound under isothermal conditions, due to vaporization, should be constant provided that the free surface area does not change [1]. Their studies attempted to correlate the rate of mass loss per unit area with vapor pressure over a wide temperature range [1]. This technique has been used by Elder to calculate the vapor pressures of pharmaceutical compounds [6]. Price and Hawkins reported the evaporation characteristics of dyes using thermogravimetry [7]. We have recently investigated such techniques for pharmaceutical solids [8,9]. Since the use of thermogravimetry is both simple and less time consuming compared to other vapor pressure measuring instruments (which will be elucidated below in this paper), there has been a plethora of data published in this field so far. The wide ranges of compounds that have been studied include complex organic pharmaceutical solids and cosmetic ingredients [10–14]. In a recent review article [15], Price addresses some of the issues connected with such a technique and its pharmaceutical implications quite comprehensively. The pharmaceutical applications of this technique could be realized in preformulation studies, when attempts are being made to characterize the basic thermodynamic properties of a poten-

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Abbreviations: TGA, thermo gravimetric analysis; DTG, derivative thermogravimetry; DTA, differential thermal analysis; α, fraction evaporated during TGA; m_i, initial mass in TGA; m_f, final mass in TGA; k_{vap}, coefficient of evaporation; , dm/dt, differential mass/differential time; T, absolute temperature; E_{vap}, energy of activation; R, universal gas constant; A_{vap}, pre-exponential factor in Arrhenius equation; k, order of reaction; $f(\alpha)$, function of fraction evaporated in TGA; β, heating rate; A, B, and C, Antoine constants in the Antoine equation; P, vapor pressure in Pa; α', vaporization constant in Langmuir equation; M, molecular weight; ΔH_{vap}, enthalpy of vaporization; P_{sat} and $P_{partial}$, saturated vapor pressure and partial vapor pressure, respectively

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tial candidate. As explained in Ref. [15], one such utility can be the calculation of solubility parameters with the enthalpy of vaporization value as obtained from this technique. The concept is still in its nascent stage and to date has only been applied to single component systems. During the course of our experiments, we have noticed certain anomalies and problems associated with such methods, which we intend to clarify in this paper. Also, this method can be approached in a 'step by step' manner, which will be elucidated in Section 3. It must be considered, however, that the traditional methods of actually measuring vapor pressure are quite precise, albeit time-consuming. Thermoanalytical techniques, such as thermogravimetry, have two main advantages: first, relatively small amounts of sample are required, and second, the actual experimental time is short. We intend to address the feasibility of using thermogravimetric methods in the swift estimation of vapor pressures for single component systems.

2. Theoretical development

2.1. Kinetics of evaporation

As a substance undergoes phase transition from liquid to vapor, determining the rate of mass loss can explain the evaporation process [16]. This is achieved by thermogravimetric analysis (TGA), using a linear rising temperature program. The TGA curve that shows a plot of mass against temperature or time is converted into a differential thermogravimetric (DTG) curve, which measures the rate of mass loss ($\mathrm{d}m/\mathrm{d}t$) vs. temperature. The shape of the DTG plot is instrumental in assigning a preliminary kinetic mechanism to the process. In the case of an ideal zero-order mechanism, the DTG plot shows a maximum value for ($\mathrm{d}m/\mathrm{d}t$) at a point where all the material is exhausted. Thus, the return of the DTG curve to the baseline is very abrupt and perpendicular in nature. The fraction evaporated (α) is calculated using the following equation:

$$\alpha = (m_\mathrm{i} - m_t)/(m_\mathrm{i} - m_\mathrm{f}) \tag{1}$$

where m_i and m_f are the initial and final masses in milligrams, respectively [16]. The mass at the specific time is represented as m_t. The data points are obtained from the rising portion of the DTG plot. If a plot of α vs. time or temperature were constructed, a sigmoidal shaped curve would be obtained. However, if evaporation occurs, the fraction evaporated would be obtained as the product of the time and the coefficient of evaporation (k_vap), which can be represented as a linear plot:

$$\alpha = (k_\mathrm{vap})t \tag{2}$$

At constant temperature, k_vap is equal to $\mathrm{d}\alpha/\mathrm{d}t$ [17]. The rate of evaporation is represented by $\mathrm{d}m/\mathrm{d}t$. For zero-order rate processes, the coefficient of evaporation can be calculated by dividing $\mathrm{d}m/\mathrm{d}t$ by the cross-sectional area of the crucible used for the sample. When $\ln k_\mathrm{vap}$ is plotted against $1/T$, a straight line is obtained [18], with a slope equal to $E_\mathrm{vap}/\mathrm{R}$, where E_vap is the activation energy of evaporation and R, the universal gas constant. Such plots are consistent with the Arrhenius equation:

$$k_\mathrm{vap} = A_\mathrm{vap}\,\mathrm{e}^{-E_\mathrm{vap}/\mathrm{R}T} \tag{3}$$

or

$$\ln k_\mathrm{vap} = \ln A_\mathrm{vap} - E_\mathrm{vap}/\mathrm{R}T \tag{4}$$

where, A_vap is the pre-exponential factor. The general reaction rate in solid-state is given by:

$$\mathrm{d}\alpha/\mathrm{d}t = kf(\alpha) \tag{5}$$

where $f(\alpha)$ is a function of α and t is the time [19]. The constant k in Eq. (5) is not analogous to k_evap. This can be related to the temperature by:

$$\mathrm{d}\alpha/\mathrm{d}T = (\mathrm{d}\alpha/\mathrm{d}t)(\mathrm{d}t/\mathrm{d}T) = [kf(\alpha)]/\beta \tag{6}$$

where β is the heating rate, in degrees per second [20]. This equation can be transformed into the form:

$$k = [(\mathrm{d}\alpha/\mathrm{d}T)\beta]/f(\alpha) \tag{7}$$

The term $f(\alpha)$ can be obtained from the tables of different mechanisms (Table 1). The results set of models are based on nucleation, diffusion, reaction order or geometrical factors of the reactant–product interface. For zero order, it is equal to one, and for first order, it is equal to $(1 - \alpha)$ [19]. Using the Arrhenius method:

$$\ln[(\mathrm{d}\alpha/\mathrm{d}T)\beta/f(\alpha)] = \ln A - E/\mathrm{R}T \tag{8}$$

A plot of $\ln[(\mathrm{d}\alpha/\mathrm{d}T)\beta/f(\alpha)]$ vs. $1/T$ can be utilized to determine the Arrhenius parameters. When determining kinetics, 'reaction order' (F1, F2, and F3) was used. Dollimore [21] and Wilburn [22] have described in great detail these equations along with their derivations and this is outside the scope of this paper. Such calculations would corroborate that the kinetics of evaporation is indeed zero order in nature, after which the method of estimating vapor pressure curves can be employed. Thus, after determining the order of the reaction, we determine the ways by which we can comprehensively estimate vapor pressure.

2.2. Vapor pressure by thermogravimetry

In moderate pressure ranges, the Antoine equation is an excellent empirical tool for the determination of vapor pressures [23]. It can be written as:

$$\log P = A - B/(T + C) \tag{9}$$

where P is the vapor pressure in Pascal (Pa), T is the absolute temperature in Kelvin (K), and A, B, and C are the empirical Antoine constants at a given temperature range, that might be obtained from vapor pressure data-charts in Stephenson and Malamowski [24]. (The Antoine constant 'A' is different from the pre-exponential factor in the Arrhe-

Table 1
Solid-state rate expressions for α vs. time curves

	$g(\alpha) = kt$	$f(\alpha) = (1/k)(\mathrm{d}\alpha/\mathrm{d}t)$
Geometrical models		
R2	$1 - (1 - \alpha)^{1/2}$	$2(1 - \alpha)^{1/2}$
R3	$1 - (1 - \alpha)^{1/3}$	$3(1 - \alpha)^{2/3}$
Diffusion mechanisms		
D1	α^2	$(1/2)\alpha$
D2	$(1 - \alpha)\ln(1 - \alpha) + \alpha$	$[-\ln(1 - \alpha)]^{-1}$
D3	$[1 - (1 - \alpha)^{1/3}]^2$	$3/2(1 - \alpha)^{2/3}[1 - (1 - \alpha)^{1/3}]^{-1}$
D4	$(1 - 2\alpha/3) - (1 - \alpha)^{2/3}$	$3/2[(1 - \alpha)^{-1/3} - 1]^{-1}$
Reaction order[a]		
F1	$-\ln(1 - \alpha)$	$1 - \alpha$
F2	$(1 - \alpha)^{-1}$	$(1 - \alpha)^2$
F3	$(1 - \alpha)^{-2}$	$1/2(1 - \alpha)^3$

[a] Method used for determining reaction order in this study.

nius equation.) It is mainly used to evaluate the temperature dependence of vapor pressure. There are two things one must take into account when utilizing this equation: first, the Antoine constants are empirical and no physical significance has been associated with them to date; and second, these constants can be used to define vapor pressures only within specified temperature ranges. For example, benzoic acid has a triplet of Antoine constants reported in the literature with three distinctly different temperature ranges. Thus, use of such constants should be carried out with caution. We have used these constants to define the vapor pressure curve for our reference compound methyl paraben, which was used for calibration of the process (the exact procedure will be elucidated in Section 3.4). The Antoine constants that have been recorded for methyl paraben are: $A = 5.23662$, $B = 1159.34$ and $C = -220.03$, for a given temperature range of 446–517 K. In a P–T plot (i.e. vapor pressure plot) the Antoine constants are used as regression parameters and therefore they do not have any physical significance. Hence, they are unitless.

The equation that relates rate of mass loss with time was first postulated by Langmuir [25] in his 1913 paper and is represented as follows:

$$\mathrm{d}m/\mathrm{d}t = (P)(\alpha')(\mathrm{M}/2\pi\mathrm{RT})^{1/2} \tag{10}$$

where $\mathrm{d}m/\mathrm{d}t$ is the rate of mass loss per unit area, P the pressure, α' the vaporization constant, T the absolute temperature, R the universal gas constant and M the molecular weight of the evaporating vapor. It is important to note that α' was denoted as the 'vaporization constant' by Langmuir and is fundamentally different from the extent of reaction (α) that has been reported in this paper. The objective in this study is to determine the vaporization constant in the presence of a purge gas, as compared to Langmuir's, where the reaction was carried out in vacuum.

Langmuir had derived Eq. (10) from the principles of kinetic theory of gases and his work involved quantifying the evaporation phenomena for metallic tungsten. Langmuir spent considerable time discussing the value of the vaporization constant and was of the opinion that it is unity if the initial conditions were those of a vacuum, but did not exclude the fact that it may have different values from unity. For the use of the Langmuir equation for the TG data, one must assume the fact that α' is a constant that is not unity in the presence of a purge gas. There are two important assumptions necessary for the Langmuir equation to be valid. First, mass loss must occur from a given container exposing a constant area of interface, and second, the coefficient of evaporation, k_{vap}, is independent of the vapor being investigated, provided it is not associated. These assumptions have been explained in great detail by Langmuir and are quite important experimentally; for example, in the experimental set up, we must maintain the evaporating surface area constant.

To apply this equation to thermogravimetric studies, we rearrange the equation as follows:

$$P = [(\alpha')^{-1}(2\pi\mathrm{R})^{1/2}][(T/M)^{1/2}(\mathrm{d}m/\mathrm{d}t)] = k_{\mathrm{vap}}\nu \tag{11}$$

where $k_{\mathrm{vap}} = \alpha'^{-1}(2\pi\mathrm{R})^{1/2}$ and $\nu = (T/M)^{1/2}(\mathrm{d}m/\mathrm{d}t)$.

Since ν would be a constant for a given compound, the slope of the plot of P vs. ν would give the value of k_{vap}. Alternatively, if we take the logarithm of the above equation, then a plot of $\log P$ vs. $\log \nu$ would give the intercept value of $\log k_{\mathrm{vap}}$ [26]. Thus, the coefficient of vaporization can be measured from the vapor pressure character of one compound and applied to other compounds whose Antoine constants have not been characterized.

It must be mentioned here that we have not taken into account the Clausius–Clapeyron equation at all while determining vapor pressures. This equation has been the classical and most widely used equation to date for the actual measurement of vapor pressures. In our study, we have not actually measured vapor pressures, but have calculated them. Hence, the use of the Clausius–Clapeyron equation would not have been accurate. We have only used this equation to calculate the heat of vaporization (ΔH_{vap})

value to corroborate that for evaporation processes, the activation energy is indeed very close to the ΔH_{vap} value. Thus, from the plot of log P vs. $1/T$, we obtained ΔH_{vap} and we did not use the Clausius–Clapeyron equation for any other purpose. The equation can be represented as follows:

$$\log(P_2/P_1) = [\Delta H_{vap}/(2.303R)][(T_2 - T_1)/T_1T_2] \qquad (12)$$

After the vapor pressure curves were constructed, we proceeded to fit those curves to evaluate the Antoine constant. For such purposes, a non-linear regression analysis is used quite often, mainly due to its flexibility and accuracy. The empirical Antoine constants for each compound can be effectively determined by the 'least square curve-fit' method, where the vapor pressure plot for each compound is fitted to the Antoine equation. The parameters A, B and C would be susceptible to changes depending on the algorithm used. For practical purposes, the Levenberg–Marquardt algorithm [27] was used and the 'global' least square fit was found to be consistently accurate in predicting the Antoine parameters. The two most important considerations during such curve fitting operations are as follows:

1. The method of statistical iterations can be easily subjected to change according to the stipulations (or constraints) applied by the experimenter [27]. Thus, after the meeting of the convergence criteria in non-linear regression iterations, it is mandatory to use the values for A, B and C and corroborate the fact that these parameters indeed describe the vapor pressure curve.
2. All statistical software used for non-linear regression purposes require a starting value for each parameter before it proceeds with the iterations. This task might be simplified if the Antoine values for one of the compounds in the homologous series, being evaluated is known. It can be expected that the unknown Antoine parameters for the compounds in study will not differ by a very large extent compared to the one in its homologous series. For the present study, the starting values stipulated in ASTM methods E1719 and E1782 have been used [28].

3. Materials and methods

3.1. Materials

Methyl paraben was obtained from Fischer Scientific Co., USA, and salicylic acid, *meta*-, *para*-hydroxy benzoic acid, anthranilic acid, *meta*-, and *para*-amino benzoic acid were all obtained from Sigma Chemical Co., USA. The purity of the compounds was in accordance with USP standards and was used as received.

3.2. Equipment

The SDT 2960, simultaneous TGA–DTA, TA Instruments, with Thermal Analyst 2000, TA operating system version 1.0 was used. An electronic flow meter from J and W Scientific, Model ADM, was used to regulate the flow of the dry nitrogen purge gas through the samples. The SPSS 10.0 software was used for statistical analyses.

3.3. Experimental set up

To comprehend the experimental set up better, we are hereby including some general attributes of the thermogravimetric instrument and outlining the important experimental variables related to the evaporation studies. Almost all thermal analysis methods use a similar apparatus arrangement [29] and thermogravimetry is no exception. The equipment enables the sample to be heated so that its temperature and one or more of its physical properties can be continuously measured and recorded. Three basic units are involved: the measuring unit must be in a particular position in the furnace; the temperature controlling unit should be simply the furnace and the programmer; and the recording unit, which receives a signal from the measuring unit and the temperature thermocouples. A controlled atmosphere must be passed around the sample and a thermocouple should be in proximity to the sample so that the temperature is accurately measured. The sample atmosphere is very important in liquid gas systems or in chemical reactions, and thus, the measuring units should be capable of operating in inert as well as reactive gas or under vacuum conditions. The most common atmosphere (purge gas) used is nitrogen for its inert nature and our study was no exception.

The temperature control unit can be a simple furnace and programmer. The recording unit receives a signal from the measuring unit and the temperature thermocouple. In most cases, this is fed into a computer, which then allows the signal to be displayed in a variety of ways, depending upon the operator [30]. Fig. 1 shows a schematic diagram of the TGA instrument.

The main factors that must be included and reported for every thermal analysis experiment are:

1. Sample: The source, pretreatment and chemical description of the sample are extremely important factors. In our study, there was no pre-treatment of samples and we used the samples as received. Also the sample weight used was always around 10 mg.
2. Crucible: The material and the geometry of the crucible, if not maintained uniformly throughout the experiment, can influence the results considerably. Change of crucible material may alter heat transfer due to different thermal conductivity. For our experiments, we had used one crucible each, uniformly, for the sample and reference crucibles, respectively. The crucibles were made of platinum and had a uniform cross-sectional area of 0.34 cm^2. The amount of solid sample in the crucible occupied about one-third of the crucible volume. The solid was loaded onto the crucible and the crucible was placed on the crucible-holder in one of the balance arms. The other

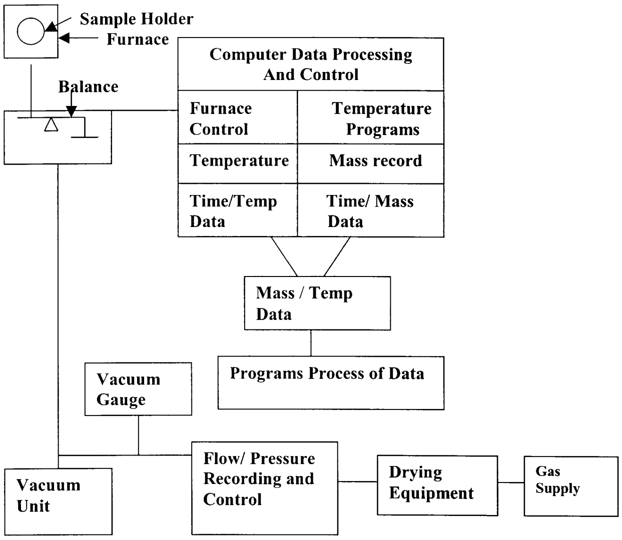

Fig. 1. A schematic diagram of a contemporary thermogravimetric unit [3].

balance arm holds the empty crucible used as reference. The assumption made is that there is no lag in heat transfer between the sample and the crucible.

3. Rate of heating: dT/dt might range from 0 °C/min (i.e. isothermal conditions) to the normal rates of 1–20 °C min^{-1}. The transfer between the furnace and the different parts of the sample are not instantaneous, but will depend on the conduction, convection and radiation that can occur within the apparatus; the higher the rate of heating, the greater the lag will be. A very rapid heating rate may melt some of the sample before it decomposes. In our study we used a heating rate of 10°C min^{-1}. After the runs, there was no sample mass left in the crucible indicating that the samples had completely evaporated.
4. Atmosphere: Transfer of heat and the chemistry of the sample reaction will depend greatly upon the atmosphere surrounding the sample and its products. During a reaction, the nature of the thermal event will change completely; while a metal may be stable in helium, it might completely oxidize in air. The flow rate of the gas also plays an important role. A fully static atmosphere will not sweep away any reaction products from the sample. The sample atmosphere was therefore chosen to be dry nitrogen at a rate of 100 ml min^{-1}. The result was that there was a continuous flow that prevented any build-up of the evaporating vapor. The clarity of the signal was satisfactory and the possibility of noise due to buoyancy effect was non-existent.
5. Mass of the sample: physical properties such as size, packing and density will alter the results obtained. The samples used in this study were free flowing and were made to occupy about one-third of the crucible volume. After the experiment, the samples were completely evaporated and there was no residue on the pan. The open-pan TGA method does not allow the build-up of reaction products, or in this case, the vapor, due to the purge gas and thus, maintains identical conditions throughout the experiment.

3.4. Experimental procedure

The methods are reported step-by-step for clarity:

1. A reference material has to be chosen that has its Antoine constants reported in the literature. For the purpose of this study, methyl paraben, the most commonly used pharmaceutical preservative, was used.
2. Methyl paraben was subjected to thermogravimetric runs under a variety of experimental conditions. The objective here is to find the condition that would result in optimum separation between the endothermic processes. In other words, the melting and sublimation processes would be distinguished clearly from one another. Nitrogen flow rates were studied at 25, 50, 80, 100 and 125 ml min^{-1}. The rates of temperature rise in the rising temperature program chosen, were 2, 5, 10 and 15°C min^{-1}. It was extremely important to determine the range of temperatures over which our calculation would hold true.
3. It was experimentally verified that the best flow rate would be 100 ml min^{-1} with the temperature rising at 10°C min^{-1}. The runs were conducted in a temperature range from ambient to 400 °C. An open, 110 μl platinum crucible with a cross-sectional area of 0.34 cm^2 was used to contain the sample and an empty platinum crucible of equivalent area was used as the reference. The sample size was 9.6 mg and all the subsequent sample sizes were maintained approximately from 8 to 10 mg. The DTA curve (not shown) showed two distinct endothermic processes of melting and sublimation, and the temperature range for evaporation was chosen.
4. The rate of loss of methyl paraben due to heat (mg min^{-1}) along with the first derivative of weight loss data was obtained from the instrument. Using the Arrhenius equation, the activation energy and pre-exponential factors were calculated. With the Antoine equation reported in the literature, the theoretical vapor pressure calculations were performed and the vapor pressure curve obtained. The k-value, from the Langmuir equation was obtained as 12 4525 ± 0.8 Pa kg$^{0.5}$ mol$^{0.5}$ s^{-1} m^{-2} K$^{-0.5}$. The run for methyl paraben was repeated three times and the average of the calculated k-value was taken. Other scientists have reported the values that are extremely close [10–14]. The hydroxy and amino benzoic acids were subjected to thermogravimetric runs under the same experimental conditions. The sample sizes for all the compounds were maintained at around 8–10 mg. Calculations for the kinetics were performed and the decomposition for *ortho* (salicylic acid) and *meta*-hydroxy benzoic acids along with anthranilic acid were determined to be zero order in nature. *meta*-Amino benzoic acid, *para*-amino and *para*-hydroxy benzoic acids followed a first-order

mechanism and therefore, were not subjected to evaporation kinetics.

5. Using the k-value obtained from methyl paraben, the vapor pressure curves for the compounds exhibiting zero-order kinetics were constructed. From the Langmuir equation, the value for (α'), the vaporization constant, was determined.
6. The Antoine constants over a specific temperature range had to be evaluated for the compounds. It was obvious that the vapor pressure curve was not linear for all the compounds studied. The Antoine equation could not be transformed into a linear form. Non-linear regression was deemed to be the best possible measure for curve fitting purposes and statistically, the Antoine constants were obtained. The Levenberg–Marquardt Algorithm was used to obtain the 'global least square fit'.
7. The Antoine parameters need to be validated and the experimental and theoretical vapor pressure data were compared with each other. They showed very close proximity, which confirmed the validity of the calculated Antoine constants over a specified temperature range for each compound. It should be mentioned here that the method of iterations is an arbitrary procedure. If different algorithms were used, there would be a different set of iterations generated. Irrespective of the algorithm used, after determining the Antoine constants, the validation step is absolutely necessary where the degree of 'goodness of fit' is validated. As long as this is achieved, any method should be valid.

4. Results and discussions

4.1. Evaporation mechanism

For the determination of evaporation characteristics, it is imperative that the loss of mass be attributable to a zero-order evaporation process. The order of the reaction is one of the first attributes to be determined. For typical zero-order reactions, the shape of the DTG curve will have a characteristic sharp, vertical decline to the baseline. Understandably, not all compounds can be expected to exhibit this trend and assumptions might lead to erroneous results. The Arrhenius parameters are to be determined from the rising curves of the DTG plots for all the compounds. The sequences of equations that lead to such analyses are elucidated from Eqs. (1)–(8) and Table 2 shows an example of such calculations with *meta*-hydroxy benzoic acid.*ortho*- and *meta*-Hydroxy benzoic acids, along with anthranilic acid follow zero-order kinetics; the remaining compounds do not and hence, they cannot be subjected to evaporation studies. The DTG plots for the hydroxy and amino benzoic acid derivatives are seen in Figs. 2 and 3, respectively. The Clausius–Clapeyron equation was utilized to evaluate the latent heat of evaporation (ΔH_{vap}) for the compounds undergoing a zero-order process and the value of ΔH_{vap}, for these compounds closely corresponds to their energy of activation values, indicating their non-activated reaction mechanism. The Arrhenius parameters are seen in Table 3. From this table we observe that the energy of activation closely corresponds to the value for the latent heat of vaporization, confirming a non-activated evaporation process. The ΔH_{vap} values obtained are also seen in Table 3. There can be a variety of reasons for which some compounds exhibit zero-order evaporation while others do not. For substituted aromatic acids, the problem becomes one of orientation. *ortho*-Hydroxy and *ortho*-amino derivatives of benzoic acids will undergo intramolecular hydrogen bonding that will form discrete molecules and initiate the process of rapid evaporation. The *para*-derivatives on the other hand will form intermolecular hydrogen bonding and greater thermal energy would be required to initiate their reaction.

Table 2
Calculations for kinetic determination of *meta*-hydroxy benzoic acid used as an example in which the rate constants are unitless[a]

T (K)	dm/dt (mg min^{-1})	1/T (K^{-1})	α	dα/dt (k_0)	$k_0/(1-\alpha)$ (k_1)	$k_0/(1-\alpha)^2$ (k_2)
493	0.9591	0.002028	0.112251	0.056843	0.06403	0.072126
494	0.9997	0.002024	0.117585	0.059249	0.067144	0.076091
495	1.044	0.00202	0.122919	0.061874	0.070546	0.080432
496	1.082	0.002016	0.128846	0.064126	0.073611	0.84498
497	1.131	0.002012	0.135365	0.067031	0.077525	0.089662
498	1.18	0.002008	0.141884	0.069935	0.081498	0.094973
499	1.226	0.002004	0.148996	0.72661	0.85383	0.100332
500	1.279	0.002	0.156108	0.075802	0.089824	0.106441
501	1.327	0.001996	0.164406	0.078647	0.094121	0.112639
502	1.385	0.001992	0.172703	0.082084	0.09922	0.119933
503	1.44	0.001988	0.181	0.085344	0.104205	0.127235
504	1.497	0.001984	0.18989	0.088722	0.109519	0.13519
505	1.563	0.00198	0.199373	0.092634	0.115702	0.144514
506	1.62	0.001976	0.209448	0.096012	0.121449	0.153626

[a] Data reported as generated by the computer prior to significant figure consideration. α = Extent of reaction as defined in Eq. (1); k_0, k_1, and k_2 are the zero-, first-, and second-order reactions rates determined experimentally; plot of natural log of the rate constants vs. 1/T shows the best fit closest to a straight line, which is the final reaction order.

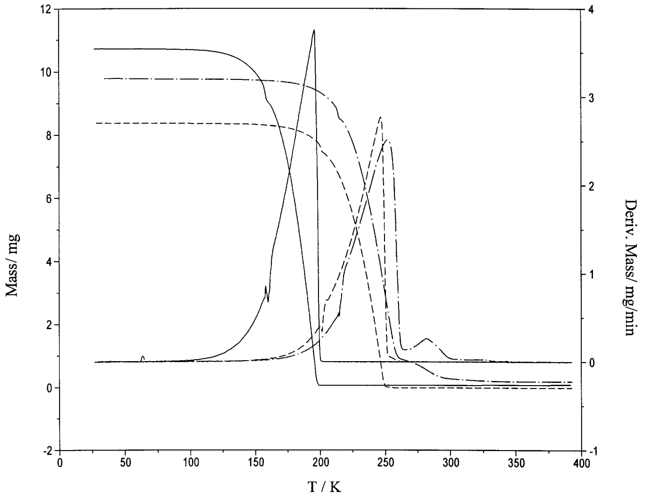

Fig. 2. TG–DTG plots for salicyclic acid (—), *meta*-hydroxy benzoic acid (- - - -), and *para*-hydroxy benzoic acid (-·-·-·).

One interesting fact that has been noted in this study is that *meta*-hydroxy benzoic acid undergoes evaporation, while the *meta*-amino derivative does not. It is a well known fact that the amino group is a stronger *ortho–para* directing group than the hydroxy group and consequently, the amino group will be a stronger deactivator of the aromatic ring in the *meta* position compared to the hydroxy group. Thus, the *meta*-hydroxy derivative is preferentially more susceptible to evaporation than the *meta*-amino variety [31].

4.2. Calculation of vapor pressures

Phang and Dollimore [10] have taken a compound whose Antoine constants are known, and used this method to compare the vapor pressure curve in the literature with that of the estimated curve. For our purposes, we chose methyl paraben as the model compound. It was taken as the calibration compound since its Antoine constants are well reported in the literature and the vapor pressure for methyl paraben was easily defined from these constants. The TG–DTG plot for methyl paraben (Fig. 4) also showed a complete zero order process. A plot of log P against log v (Fig. 5) was used to obtain the value of (k) from the Langmuir equation. The value for this coefficient of evaporation (k), obtained from methyl paraben, was determined to be 12 4525 ± 0.8 Pa $\mathrm{kg}^{0.5}\,\mathrm{mol}^{0.5}\,\mathrm{s}^{-1}\,\mathrm{m}^{-2}\,\mathrm{K}^{-0.5}$ (Table 4 shows an example of such calculations with salicylic acid). Fig. 6 shows the vapor pressure curves for the compounds undergoing evaporation. In all the TG–DTG curves, a characteristic 'bump' is observed much before appreciable weight loss is observed. This apparently unexplained phenomenon (there is no evidence in the literature explaining this to date) is probably due to the stabilization of the TGA signal since we observe this on all the outputs; however, this had no effect on the final results.

4.3. Calibration

The coefficient of vaporization (k) is perhaps the most important parameter in the Langmuir equation that is being utilized in such studies. This parameter is a constant, and is independent of the material being studied. This is the basic assumption that must be followed in order to apply the k-value to calculate vapor pressures of unknown compounds. In this study, the value of k was obtained as $1.2 \times 10^5 \pm 0.8$ Pa $\mathrm{kg}^{0.5}\,\mathrm{mol}^{0.5}\,\mathrm{s}^{-1}\,\mathrm{m}^{-2}\,\mathrm{K}^{-0.5}$. This is in good correlation with the reported value of k [10–14]. The units of k can also be expressed in units different from above, though non-uniformity might lead to confusion in certain cases. Experimental factors may also alter the k-value, such as the flow rate of nitrogen and the heating rate, but these factors were not investigated in this study.

4.4. The value of α'

From the Langmuir equation, it can be observed that the k-value is inversely proportional to α'. Langmuir had suggested that the value of α' is unity under vacuum conditions [25], though he did not categorically state that it could not change under the influence of a purge gas. It is important to note that the experimental design utilized in this study would have a multicomponent atmosphere. First, there is nitrogen as the purge gas and second, the compound being investigated is itself vaporizing and continuously adding to the partial pressure of the material. This expectedly would alter the value for α'. However, the value of α is obtained as $5.8 \times 10^{-5}\ \mathrm{Pa}^{-1}\,\mathrm{mol}^{-1}\,\mathrm{m}^{-3}$. This extremely small quantity is very difficult to explain with the resources available. However, we believe that it is the impurity of the sample that influences the vaporization constant. The purity grades of the samples studied were according to USP specifications, but even an extremely small percentage of impurity can be magnified many fold when the evaporation interface

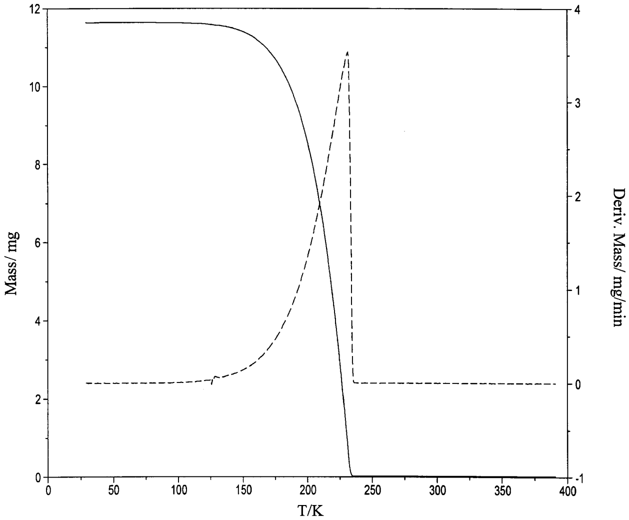

Fig. 3. TG (—) and DTG (- - -) plot for methyl paraben.

Table 3
Calculations for vapor pressure of salicylic acid used as an example[a]

T (K)	$(\mathrm{d}m/\mathrm{d}t)/A$ (kg m^{-2} s^{-1})	$(T/M)^{0.5}$ (s$^{0.5}$ kg$^{-0.5}$)	ν	k[b]	P	α
441	0.000672	56.50544	0.037947	124525	5221.175	6.42163×10^{-5}
442	0.000703	56.56957	0.039793	124525	5475.092	6.3755×10^{-5}
443	0.000734	56.63352	0.041559	124525	5718.104	6.36851×10^{-5}
444	0.000768	56.69741	0.043524	124525	5988.412	6.30828×10^{-5}
445	0.000802	56.76122	0.045548	124525	6266.963	6.29436×10^{-5}
446	0.000838	56.82496	0.047605	124525	6549.949	6.29436×10^{-5}
447	0.000873	56.88863	0.049666	124525	6833.546	6.248×10^{-5}
448	0.000947	56.95223	0.051648	124525	7106.228	6.22101×10^{-5}
449	0.000947	57.01576	0.053969	124525	7425.64	6.2116×10^{-5}
450	0.000986	57.07921	0.056296	124525	7745.735	6.1679×10^{-5}
451	0.001029	57.1426	0.058823	124525	8093.493	6.14873×10^{-5}
452	0.001074	57.20591	0.061412	124525	8449.709	6.14889×10^{-5}
453	0.001114	57.26916	0.06381	124525	8779.645	6.1127×10^{-5}
454	0.001162	57.33234	0.066635	124525	9168.281	6.1185×10^{-5}
455	0.00121	57.39544	0.069465	124525	9557.74	6.08938×10^{-5}

[a] Data reported as generated by the computer prior to significant figure consideration.

[b] k = Value of coefficient of evaporation, obtained from methyl paraben.

is, in fact, a capillary-like thin film of solid. Moreover, in the melt, the impurity would migrate to the surface and this might lead to considerable differences in the value for α'. This is one aspect that would require resolution by further investigation.

4.5. Mass transfer

To document the true meaning of our measurements, we can refer to a general mass transfer mechanism for thermogravimetric experiments:

$$\mathrm{d}m/\mathrm{d}t \propto (P_{\mathrm{sat}} - P_{\mathrm{partial}})$$

where $\mathrm{d}m/\mathrm{d}t$ is the rate of mass loss, P_{sat} the saturated vapor pressure (which we want to measure as P in the Langmuir equation), and P_{partial} the partial vapor pressure on top of the pan. With the use of nitrogen as the purge gas, we want to reduce the partial pressure to almost 0; this is where zero order is validated and the evaporation rate is independent of the sample remaining on the pan. Though the above mass-transfer relationship, in general, is very close to the Langmuir equation, mass transfer has not been used exclusively for analysis. This is due to the fact that a very small sample mass is being used and mass transport is occurring at a very rapid rate. Use of the Antoine and Langmuir equations seemed appropriate for the method adopted in our study.

4.6. Curve fitting for Antoine constants

The method of non-linear regression was used for the determination of the unknown Antoine constants. The

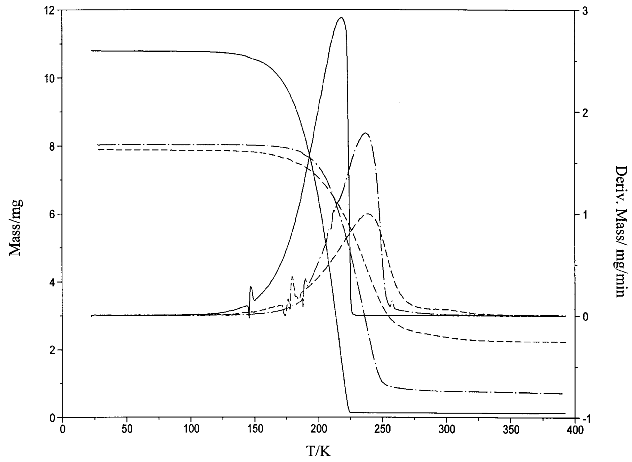

Fig. 4. TG–DTG plots for anthranilic acid (—), *meta*-amino benzoic acid (- - -), and *para*-amino benzoic acid (-·-·-·).

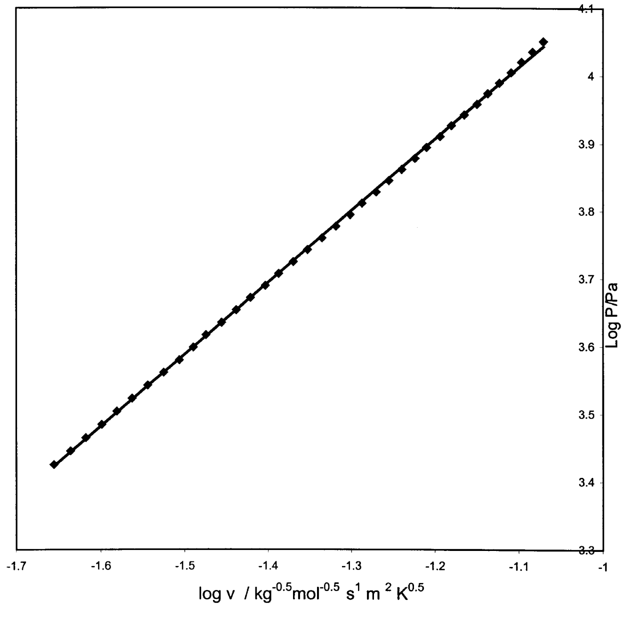

Fig. 5. Calculation for the coefficient of evaporation (k); plot of log P vs. ν, where the intercept is 5.1793; slope = 1.061 and R^2 is 0.998.

Table 4
Summary of the values for E_{act} and ΔH_{vap} for the compounds studied

Compound	E_{act} (kJ mol^{-1})[a]	ΔH_{vap} (kJ mol^{-1})
Methyl paraben	75.1	77.1
ortho-Hydroxy benzoic acid	64.8	66.7
meta-Hydroxy benzoic acid	78.2	80.4
para-Hydroxy benzoic acid	119.1	–
ortho-Amino benzoic acid	76.9	79.9
meta-Amino benzoic acid	90.68	–
para-Amino benzoic acid	118.32	–

[a] For compounds undergoing zero-order evaporation process, the energy of activation is very close to the latent heat of evaporation value, signifying a non-activated process.

Table 5
List of Antoine constants for compounds undergoing evaporation

Compound	Antoine constants			ΔT (K)
	A	*B*	*C*	
Methyl paraben[a]	5.23	1159.34	−220.03	446–499
ortho-Hydroxy benzoic acid	6.28	316.74	−319.88	441–477
meta-Hydroxy benzoic acid	6.35	374.47	−360.21	493–537
ortho-Amino benzoic acid	5.36	97.22	−397.84	453–491

[a] Antoine constants reported in literature; constants *A*, *B*, and *C* are unitless.

Antoine equation cannot be linearized without making some bold assumptions and such assumptions might not be valid over a large temperature range. Therefore, non-linear regression was deemed to be the best method to use in this instance. The SPSS 10.0 software was used and the Levenberg–Marquardt algorithm for the global least square fit was applied. In order to compute iterations for non-linear regression, one has to specify the starting parameters for the Antoine constants. ASTM methods E1719 and E1782 specify the starting values for *A*, *B* and *C* to be 9.3, 2000 and −37, respectively, when the pressure is in Pa and temperature is in K [28]. For the list of compounds studied, these values proved to be useful as they generated acceptable curve fits (Table 5). It should be pointed out here that the values *A*, *B*, and *C* are unitless and are considered to be empirical constants. The method described in this study gives an acceptable estimate for the Antoine constants, when we compare the results for compounds whose experimental vapor pressure is known (data not shown). Benzoic acid, for example, is a compound whose Antoine constants are reported in the literature; the calculated Antoine constants for benzoic acid by the method described in this paper were in good agreement with the literature data.

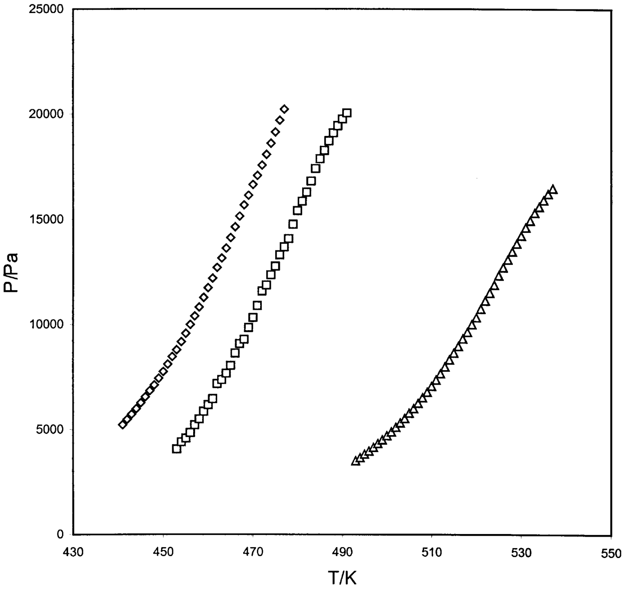

Fig. 6. Vapor pressure plots for salicyclic acid (◇), *meta*-hydroxy benzoic acid (△), and anthranilic acid (□).

5. Conclusions

It is mandatory that pre-formulation efforts during the basic physico-chemical characterization of a new drug candidate be efficient and reasonably rapid in nature. Estimating thermodynamic properties (for example, solubility) requires good estimates for enthalpies of vaporization and energies of activation for the particular compound. In this paper, we have presented some baseline efforts to simplify such endeavors by a simple and rapid technique. For single component systems that have been tested, this method works well within reasonable acceptance limits and gives vapor pressure values, which have good agreement with values reported earlier by traditional measurements. This method can also be used in a more general way for any chemical ingredient undergoing zero-order evaporation process.

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