ELSEVIER

International Journal of Pharmaceutics 213 (2001) 31–44

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

A new application for the Antoine equation in formulation development

Koustuv Chatterjee, David Dollimore, Kenneth Alexander *

College of Pharmacy and Department of Chemistry, The University of Toledo, Toledo, OH 43606, USA

Received 6 June 2000; received in revised form 19 September 2000; accepted 16 October 2000

Abstract

Characterization of formulation components in pre-formulation and formulation studies will be made easier if a rapid method to evaluate the evaporation characteristics of an ingredient in the formulation is developed. This study aims at providing a simple and rapid thermogravimetric method for estimating the vapor pressure characteristics using the Antoine equation as the analytical tool. The heat treatment for the majority of benzoic acid derivatives follows zero-order rate processes that are in good correlation with their evaporation process. The optimum conditions for the rising temperature experiments were found when the heating rate was 10°C/min in an atmosphere of dry nitrogen (100 ml/min). Methyl paraben was taken as the calibration compound since its Antoine constants are reported in the literature, and its selected thermodynamic parameters were evaluated using the Langmuir equation. The coefficient of vaporization ($\underline{k}$) was determined to be 124 525 $\pm$ 0.8, with units being reported in the S.I. system. The corresponding vapor-pressure plots were obtained for the remaining compounds and their Antoine constants calculated.

Keywords: Antoine equation; Langmuir equation; Parabens; Thermogravimetry; Vapor pressure

1. Introduction

Benzoic acid derivatives find wide application in the pharmaceutical industry. Para-hydroxy benzoic acid esters are commonly used as preservatives for their pronounced anti-microbial activity. The methyl, ethyl, propyl and butyl esters are the most common compounds used and are all obtained as white crystalline powders. These preservatives differ in a variety of their properties ranging from their minimum inhibitory concentrations to their relative effectiveness in aqueous or oleaginous media. Many formulations contain a mixture of two or more preservatives to minimize the adverse effects of high concentrations of one single preservative.

The benzoic acid moiety is in itself one of the most ubiquitous entities among the chemical structures of many pharmaceuticals. Salicylates, para-amino benzoic acid derivatives (PABA), the amino benzoates, the phthalates, etc., form the

* Corresponding author. Tel.: +1-419-5301988; fax: +1-419-5301950.

E-mail address: kalexan@uoft02.utoledo.edu (K. Alexander).

0378-5173/01/$ - see front matter
PII: S0378-5173(00)00644-X

core of most antibiotics, analgesics, antipyretics and other categories of drugs. Therefore, it is necessary that for a given formulation, the individual component evaporation characteristics be determined and quantified. During the initial phase of characterization, the thermodynamic parameters (e.g. enthalpy of fusion, etc.) need to be quantified, and a vapor pressure plot might be essential. Most pharmaceutical preparations undergo heat treatment during accelerated stability testing or in their shelf life, necessitating their accurate thermal characterization. During such analyses, there exists an underlying assumption that all the ingredients in the formulation exist in the same physical form at elevated temperatures as they do at ordinary room temperature. This assumption needs to be validated with proper vapor-pressure characterization. There might be instances in which at elevated temperatures, the ingredients, having low melting points, vaporize, thus leading to a change in the composition of the formulation. The presence of various additives might in fact lower the melting point of a single component in the formulation. Such a phenomenon might call for a modification of the currently accepted method of stability analysis for that particular compound. The purpose of this study is to examine the behavior of selected benzoic acid derivatives, construct their individual vapor-pressure plots using thermogravimetry, and validate a general method, which could be utilized for the same purpose for any formulation ingredient that exhibits evaporation characteristics.

Evaporation can be stated to be the transition from the liquid phase to the vapor phase, without a change in chemical composition. Factors such as the vapor pressure of the substance, molecular weight, amount of exposed surface area, etc. can alter the evaporation patterns. The primary influencing factor, however, is the rising temperature conditions under which the preservatives are being subjected. The evaporation parameters can be determined by the rate of mass loss as the substance undergoes a phase transition from liquid to vapor. This can be achieved with a rising temperature program in thermogravimetric analysis (Haines, 1995).

Dollimore and O'Connell (1998) have reported the kinetics of three preservatives to be zero order. Aggarwal et al. (1997) have reported the kinetics of methyl benzoate as zero order in nature. In thermogravimetry, data obtained from the Thermo Gravimetric Analysis (TGA) curve are converted into a Derivative Thermo Gravimetric (DTG) plot to obtain the rate of mass loss with temperature or time. For this process to be zero order in nature, the DTG plot must show a maximum value for the rate of mass loss at the point where the mass of the material is exhausted. This would cause an abrupt return of the rate of mass loss curve to a zero baseline. Experiments carried out in this study had all the characteristics as described above. Thus, it was assumed that all the preservatives under study are undergoing zero-order kinetics. Further, in all non-activated evaporation kinetics, the energy of activation (E_{act}) has a value very close to the enthalpy of vaporization (ΔH_{vap}) value.

1.1. Conventional methods for vapor-pressure determination

Several attempts have been made in the past to develop and validate methods for vapor-pressure measurements. Direct measurements with a mercury manometer were perhaps the starting point (de Kruif et al., 1981), followed by boiling-point determinations under reduced pressures (McDowell et al., 1973). The use of mass spectrometry to monitor the gas-phase concentration of the volatile species has been reported (Riberio da Silva et al., 1990), and of late, measuring sample volatilization by vacuum diffusion in a Knudsen cell has been studied in considerable detail (Goodrum et al., 1996).

Guckel et al. (1974) were probably the first to demonstrate the use of thermogravimetry in studying vaporization where they had measured the volatilization rates of pesticides at ambient pressures, using isothermal thermogravimetry. The main principle governing such an experiment is that since evaporation and sublimation are zero-order processes, the rate of mass loss of a compound under isothermal conditions due to vaporization should be constant, providing that

the free surface area does not change. Such studies attempted to correlate the rate of mass loss per unit area with the vapor pressure over a wide temperature range. Elder has recently used this technique to calculate the vapor pressures for pharmaceutical compounds (Elder et al., 1997). Price and Hawkins have reported the evaporation characteristics of dyes, using thermogravimetry (Price et al., 1998). Furthermore, the use of thermogravimetry, coupled with Differential Thermal Analysis and Differential Scanning Calorimetry, is a well-established method in determining thermodynamic entities such as the heat of fusion and the melting point, which substantiates the use of thermogravimetry as an important tool in the characterization of chemicals and pharmaceuticals. This study aims at providing the outline for a swift, comprehensive characterization of compounds by calculating the vapor-pressure curves and obtaining the Antoine constants for compounds undergoing evaporation.

The main advantages of the thermogravimetric method used to construct vapor pressure curves can be summarized as follows:

1. Minute amounts of the sample are required; normally, this amount ranges from 5 to 10 mg.
2. The effective experiment time is relatively short.
3. The validation with the actual experimental results, calculated by traditional methods, is quite precise.

1.2. Antoine equation

In a moderate pressure range, the Antoine equation (Majer et al., 1989) is an excellent empirical tool, primarily used for curve-fitting purposes. It can be written as:

$$\ln P = a - b/(T + c) \quad (1)$$

where (P) is the vapor pressure, (T) is the absolute temperature, $a = 2.303A$, $b = 2.303B$, and $c = C$, while A, B, and C are the Antoine constants over a given temperature range, obtained from Stephenson and Malamowski (1987). It is mainly used to evaluate the temperature dependence of vapor pressure. The Antoine constants have been recorded for methyl paraben, and the values reported are: $A = 5.23662$, $B = 1159.34$ and $C = -220.03$, for a given temperature range of 446–517 K. One of the major limitations of the Antoine equation, however, is that the constants are applicable only in the specific temperature range. To define a curve outside these limits, there should be another set of Antoine constants. For example, the Antoine constants for benzoic acid, reported in the literature comprise two sets of three constants in each (Stephenson and Malamowski, 1987). This is due to the fact that benzoic acid first sublimes, followed by evaporation, thus necessitating two sets of constants to define the two processes (data not shown). The value of P was obtained at each temperature point from 446 to 501 K, the temperature range being decided upon from the rising portion of the DTG curve.

1.3. Langmuir equation

The Langmuir equation (Shen and Alexander, 1999) can explain the evaporation phenomenon:

$$dm/dt = (P)(\alpha)(M/2\pi RT)^{1/2} \quad (2)$$

where (dm/dt) is the rate of mass loss per unit area, (P) is the pressure, (α) is the vaporization constant, (T) is the absolute temperature, (R) is the universal gas constant and (M) is the molecular weight of the evaporating vapor. The objective is to determine the vaporization constant in the presence of a purge gas.

Langmuir spent considerable time evaluating the value of the vaporization constant and was of the opinion that it should be unity if the initial conditions were those of a vacuum but did not exclude the fact that it may have different values from unity (Langmuir, 1950). In order to use the Langmuir equation for thermogravimetric data, one must assume the fact that (α) is a constant that is not unity in the presence of a purge gas. The Langmuir equation holds true for a certain rate of mass loss in volatilization from a given container exposing a constant area of interface. It depends on the experimental set-up and is independent of the vapor being examined, provided it is not associated.

Eq. (2) can be rewritten as:

$$P = [\alpha^{-1}(2\pi R)^{1/2}][(T/M)^{1/2}(\mathrm{d}m/\mathrm{d}t)] = \underline{k}v \quad (3)$$

where $\underline{k} = \alpha^{-1}(2\pi R)^{1/2}$ and $\nu = (T/M)^{1/2}$ $(\mathrm{d}m/\mathrm{d}t)$.

Since (v) would be a constant for a given set of experiments, the plot of P versus v would give the value of $(\underline{k})$. Alternatively, if we take the logarithm of Eq. (3), then a plot of log P versus log v would give the value of log $\underline{k}$. The Langmuir equation is admittedly not perfect, as it is applicable over a finite range of temperature and pressure for compounds. To start off with, the application of this equation has been made for compounds, which are similar in chemical nature and bonding characteristics. No attempt should be made at this point to extrapolate the conditions to chemical structures that differ widely. The compounds in this study are all derivatives of benzoic acid and are similar not only in their basic structure but also in the pattern of their ring substitutions.

In the set of experiments performed, the instrument was calibrated with methyl paraben as the standard, which gave the value of $(\underline{k})$. The pressure vs. temperature plot was performed. This coefficient of vaporization value thus obtained would be theoretically constant and independent of the substance used. This value was then used for ethyl, propyl and butyl parabens. Eq. (3) could be effectively utilized for each substance as the (v) for each substance would be a constant, and substituting the $(\underline{k})$ value would give the corresponding pressure values at each temperature. The vapor pressure plots were then obtained from the data. It should be noted here that the compounds under study should be chemically similar to the compound used to calibrate the instrument.

1.4. Clausius–Clapeyron equation

The enthalpy of vaporization $(\Delta H_{\mathrm{vap}})$ can be calculated for each of the compounds from the Clausius–Clapeyron equation, the final form of which is as follows:

$$\log(p_2/p_1) = [\Delta H_{\mathrm{vap}}/(2.303R)][(T_2 - T_1)/T_1T_2] \quad (4)$$

where (p_2) and (p_1) are the corresponding vapor pressures at temperatures (T_2) and (T_1), respectively, and (R) is the universal gas constant.

For all practical purposes, The Clausius Clapeyron equation can be simplified to

$$\log\ P = [\Delta H_{\mathrm{vap}}/(2.303R)][1/T]. \quad (5)$$

The plot for log P versus $1/T$ would easily generate the value for ΔH_{vap} for each compound. Classically, this equation has been very useful in cases where the vapor pressure curves for compounds have actually been measured. However, in this study, the vapor pressures were calculated by an indirect method, and the use of this equation might be limited. This point is discussed in detail in a subsequent section of this paper.

1.5. Curve fitting for calculating Antoine constants

Non-linear regression analysis is a useful tool for curve-fitting purposes. 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 (Bardsley et al., 1995) 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 (Bardsley et al., 1995). 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 are known. The unknown Antoine parameters for the compounds in the study would not be

expected to differ by a very large extent compared to that in its homologous series. For the present study, the starting values stipulated in ASTM methods E1719 and E1782 have been used (ASTM, 1997).

2. Experimental

2.1. Materials

Methyl paraben (laboratory grade) was obtained from Fisher Scientific Company (lot # 762258); ethyl paraben was obtained from Ruger Chemical Co. (lot # 1656K); propyl paraben was obtained from Sigma Chemical Co. (lot # 31F0416); butyl paraben was obtained from Sigma Chemical Co. (lot # 128F0389); salicylic acid was obtained from Sigma Chemical Co. (lot # 52H3418); and anthranilic acid was obtained from Sigma Chemical Co. (lot # 82H0406). Their purity grades were stipulated according to USP specifications and were used as received.

2.2. Equipment

The SDT 2960 simultaneous TGA-DTA, from TA instruments, with Thermal Analyst 2000 TA operating system version 1.0 was employed to investigate the evaporation behavior of the parabens. An electronic flow meter from J&W Scientific, model ADM 1000 was used to regulate the flow of dry nitrogen (purge gas) through the samples. The SPSS version 10.0 software was used to perform non-linear regression analysis.

2.3. Procedure

Rising-temperature experiments were performed on the sample, and readings were taken at every 1°C to provide accuracy to the results. The runs were conducted in a temperature range from ambient to 400°C. The heating rate was fixed at 10°C/min. Nitrogen was used as the purge gas, and its flow rate was fixed at 100 ml/min. These experimental conditions were chosen as optimum parameters that would separate the thermodynamic processes in the system. From the DTA plot (data not shown), the melting, evaporation or sublimation phase (if any) would be observable as distinct, well-separated events (endotherms and exotherms). This would ensure minimum overlap and would validate the choice of datapoints only from the rising portion of the DTG curve. An open 110 μ, 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 chosen so as to cover the base of the crucibles uniformly and to about one-third of its capacity.

Data from the DTG plot for methyl paraben were used to obtain the loss of weight for the compound for every degree Celsius rise in temperature. The Antoine and Langmuir equations were used successively to obtain the k value. Since this was to be the calibration experiment and the k value was to be taken as a constant for the successive experiments, the experiment was repeated three times to obtain the most statistically significant value for k. This was utilized to obtain the vapor-pressure values for ethyl, propyl and butyl parabens along with salicylic and anthranilic acid. The vapor-pressure plots were constructed for each of these substances. Statistical curve fitting was done for each vapor-pressure plot, and the Antoine constants were calculated for a specific temperature range. Fitting them to the vapor pressure curve corroborated the parameters so obtained. Clausius–Clapeyron plots were constructed for each compound, and the R^2 value was calculated for each plot.

3. Results and discussion

The molecular weights and the melting points for the four parabens were obtained from the literature (Wade and Weller, 1994), and the melting points were corroborated from the actual experiments with considerable precision (Table 1). Using the TG-DTG curve for methyl paraben (Fig. 1), the data points for the evaporation pattern were obtained. After performing the required calculations with the Antoine and Langmuir

equations, the plot of P versus v was obtained (Fig. 2). The k-value was obtained as 124525 ± 0.8 using the S.I. system of units, and the value of (α) was calculated to be 5.8×10^{-5}. The pressure (in Pascals) vs. temperature (in Kelvin) plot for methyl paraben was obtained (Fig. 3).

Using the above procedure as a system for calibrating the process, the remaining calculations were carried out. From the TG-DTG curve for ethyl paraben (Fig. 4), using the value obtained from the calibration experiment, the pressure versus temperature curve was obtained. Similar procedures were followed for propyl and butyl parabens. The TG-DTG plots for propyl and butyl parabens are shown in Fig. 4. The pressure versus temperature plots for ethyl, propyl and butyl parabens can be seen in Fig. 5. The TG-DTG curves for salicylic acid and anthranilic acid are given in Fig. 6, and their vapor pressure curves are shown in Fig. 7. The Clausius–Clapeyron plots are shown in Fig. 8. Non-linear regression was used, and the Antoine constants were obtained for each of the five compounds. The starting values for the constants A, B, and C were

Table 1
Physico-chemical properties of the compounds studied

Compound	Molecular formula	Melting point (°C)	Molecular weight (g/mol)
Methyl paraben	$C_8H_8O_3$	125–128	152.15
Ethyl paraben	$C_9H_{10}O_3$	115–118	166.18
Propyl paraben	$C_{10}H_{12}O_3$	95–98	180.20
Butyl paraben	$C_{11}H_{14}O_3$	68–72	194.23
Salicylic acid	$C_7H_6O_3$	158	138.12
Anthranilic acid	$C_7H_7NO_2$	146.5	137.14

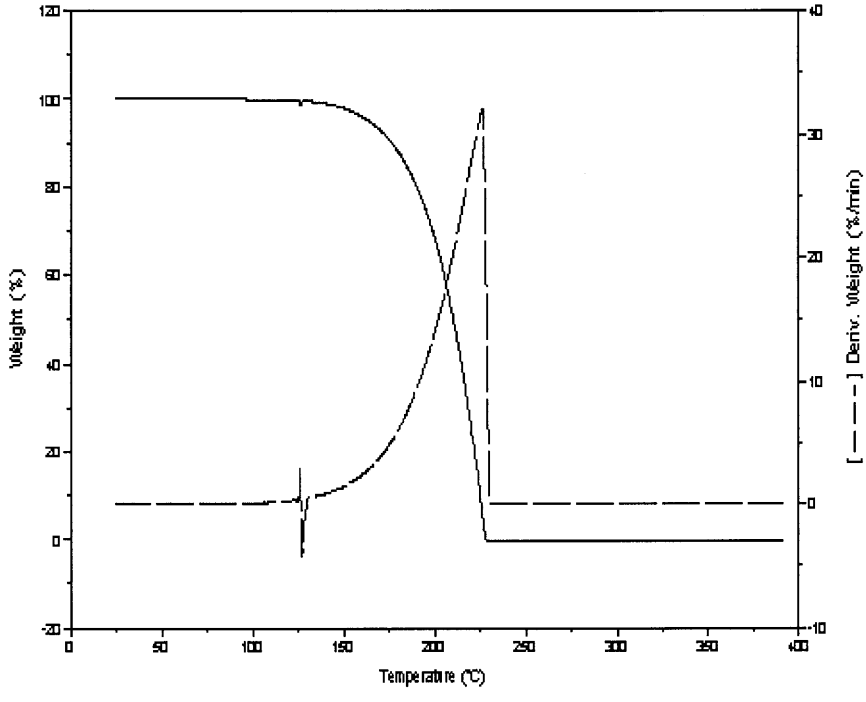

Fig. 1. TG-DTG plot for methyl paraben [(—) TG (---) DTG].

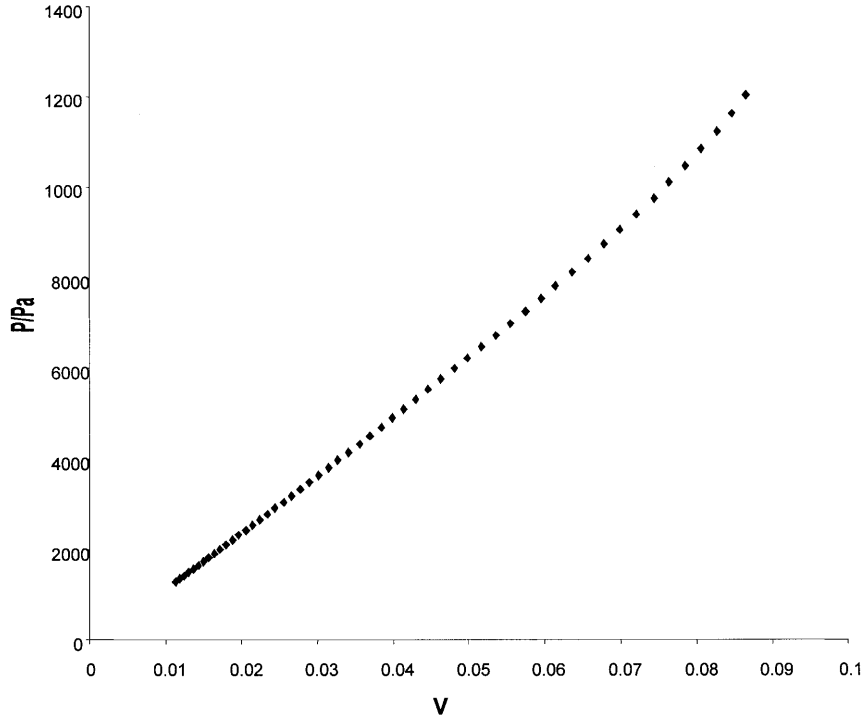

Fig. 2. Plot of P vs. v, the slope of which determines the k-value for the Langmuir equation.

9.3, 2000 and -37, respectively, the values being valid for pressure in Pascals and temperature in Kelvin. The curves generated by the calculated Antoine constants were compared with the actual vapor-pressure curves that were estimated from thermogravimetric data. Acceptable agreement was obtained, proving that the Levenberg–Marquardt algorithm (Bardsley et al., 1995) utilized for the process is adequate. The Antoine constants are given in Table 2.

Langmuir had theoretized that the value of (α) should be unity (Langmuir, 1950). However, he did not exclude the possibility that it could have other values as well. An interesting feature of this study is that the conversion of all the units to the S.I. system gives a considerably large k-value that makes the (α) value small. Moreover, the value of unity for (α) might hold true in a vacuum, but in the presence of a purge gas, it might change considerably. In this case, the purge gas was dry nitrogen. This constant might be useful in calculating the vapor pressure of related substances as well since it assumes the independence of the material used provided that there is no inter- or intramolecular association.

3.1. Importance of units

Price and Hawkins (Price et al., 1998) have studied the evaporation parameters for dispersed dyes and have reported that the relationship ($p = 0.1274v$) holds true for a series of compounds. The reported k-value was derived with the units of pressure in Pascals and v in $g^{0.5}$ $mol^{0.5}$ min^{-1} m^{-2} $K^{-0.5}$ with the rate of mass loss per unit area expressed as mg min^{-1} m^{-2}. In this study, all the units were kept uniformly in the S.I. units to eliminate confusion. It must be mentioned, however, that after converting the data obtained in this study to the units used by Price and Hawkins, it was observed that the k-value was in close agreement with that reported.

3.2. Value of k

The coefficient of vaporization (k) is perhaps the most important parameter in the Langmuir equation being utilized in such studies. This parameter is a constant and is independent of the material being studied. In this study, it was deemed best to use S.I. units in a uniform manner, and the value for k was found to be $124\ 525 \pm 0.8$. This is in good correlation with the reported value of k in the literature (Shen and Alexander, 1999). This study confirms that it is prudent to keep the units in the S.I. system, and thus the value of k is in the vicinity of 1.2×10^5. The value of k will not change, provided the entity of the purge gas is kept constant. In the present study, the purge gas was nitrogen, chosen for its relative inertness. If the components are oxidizable, then gases like oxygen, which are prone to react, should not be chosen for the study. One factor that might change the k-value is the accuracy with which the data points are chosen. As mentioned earlier, the experimental parameters, namely heating rate and flow rate of the purge gas, should be chosen such that different thermodynamic events should be uniquely visible in the Derivative Thermal Analysis (DTA) plot. For example, if the melting and evaporation endotherms overlap in the DTA plot, then it would be difficult to choose data points for evaporation alone, and the accuracy in the final results will be affected. Thus, the experimental parameters do not directly determine the k-value, but it is prudent to optimize them, nevertheless.

3.3. Value of α

In the Langmuir equation, the k-value is inversely proportional to (α). Langmuir had opined that the value of (α) is unity under vacuum conditions (Langmuir, 1950), though he did not state categorically 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

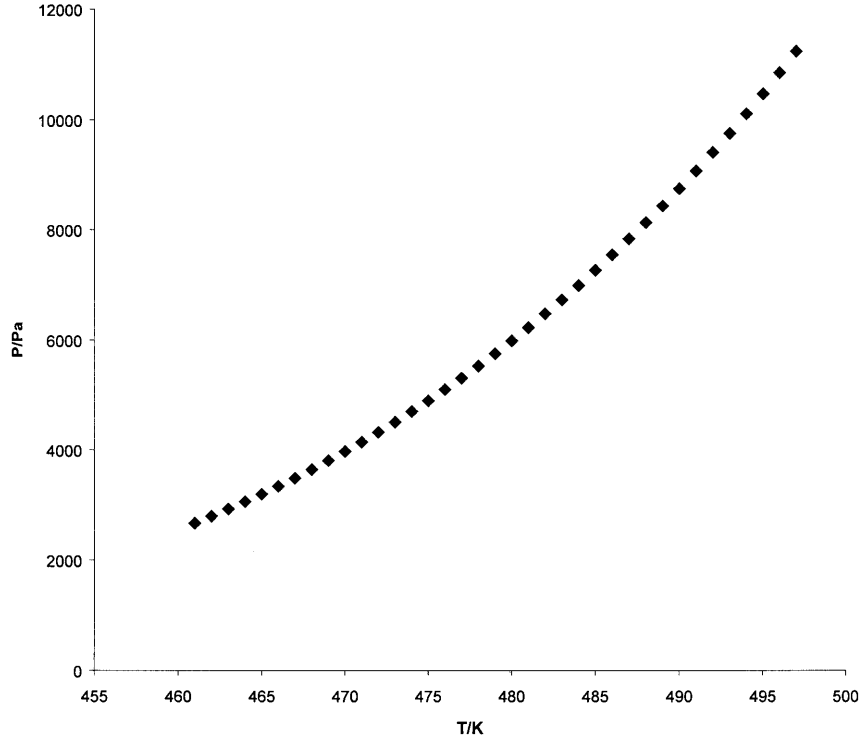

Fig. 3. Vapor pressure plot for methyl paraben.

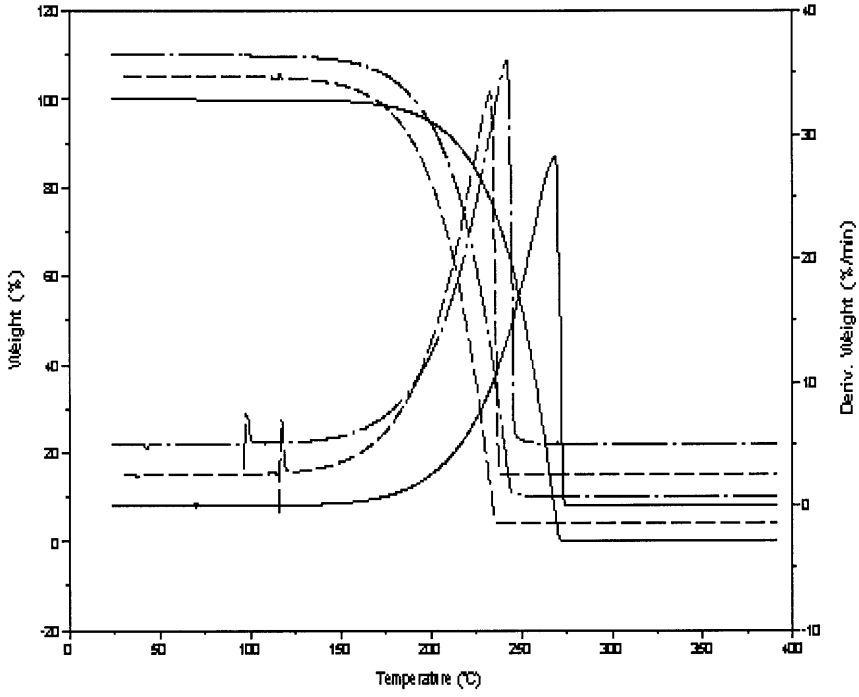

Fig. 4. TG-DTG plots for ethyl (---), propyl (-·-·-), and butyl (—) parabens.

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 would be expected to alter the value for (α). However, the value of α is found to be 5.8×10^{-5}. This extremely small quantity cannot be explained yet with the resources currently available. Further research should be performed in this direction to critically evaluate the value of α.

3.4. Clausius–Clapeyron plots

Clausius–Clapeyron plots were generated for each compound in the study. Such plots have log P (logarithm of pressure) in the y-axis and the reciprocal of absolute temperature ($1/T$) in the x-axis. Those compounds that exhibited zero-order evaporation processes were taken into consideration, and their Clausius–Clapeyron plots were generated (Fig. 8). The validity of the Clausius–Clapeyron plots is unquestionable when the vapor pressures of the compounds are actually being measured experimentally. It should be noted that in the present study, the vapor pressures were not actually measured experimentally but estimated by an indirect, calculation-intensive method. When the Clausius–Clapeyron plots were generated, it was observed that the plots generated a curve rather than a straight line. If the plot is curvilinear in nature, fitting a straight line for regression parameters is futile. For the regression parameters and R^2-value to have any significance, the points must be perfectly scattered in nature. Ethyl paraben, butyl paraben, salicylic acid, and anthranilic acid have very pronounced curvilinear trends. This suggests that the Clausius–Clapeyron equation will not be ideal in constructing vapor-pressure plots, since it does not always obey the basic assumption of any statistical operation, which presupposes the random scatter of points. We stress, however, that this phenomenon is observed when the vapor pressures are only calculated, not measured, as in this present study. Therefore, the Antoine equation has a better

statistical significance when vapor-pressure curves are to be constructed from the indirect method presented in this study.

3.5. Starting block for iterations

In order to compute iterations for non-linear regression, one has to specify the starting parameters for the Antoine constants. This might not be always an easy task. 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 Pascals, and the temperature is in Kelvin (ASTM, 1997). For the list of compounds studied, these values proved to be useful as they generated acceptable curve fits. If these values did not prove to be useful, one had to take into consideration a different algorithm in order to arrive at acceptable curve fits. Operating with the same parameter constraints would be valid only if the compounds under study were chemically similar in nature. Two compounds having totally different chemical entities might not follow the same analogies when their vapor pressure curves are verified for suitable curve fits.

3.6. Pharmaceutical utility of the method investigated

The initial physical characterization of a pharmaceutically active compound involves the calculation of the thermodynamic parameters like enthalpy of fusion, sublimation, etc., and the melting and subsequent evaporation characteristics of the compound have to be determined. In pre-formulation and formulation development, the vapor pressures for the compounds under study are calculated as this generates the vapor-

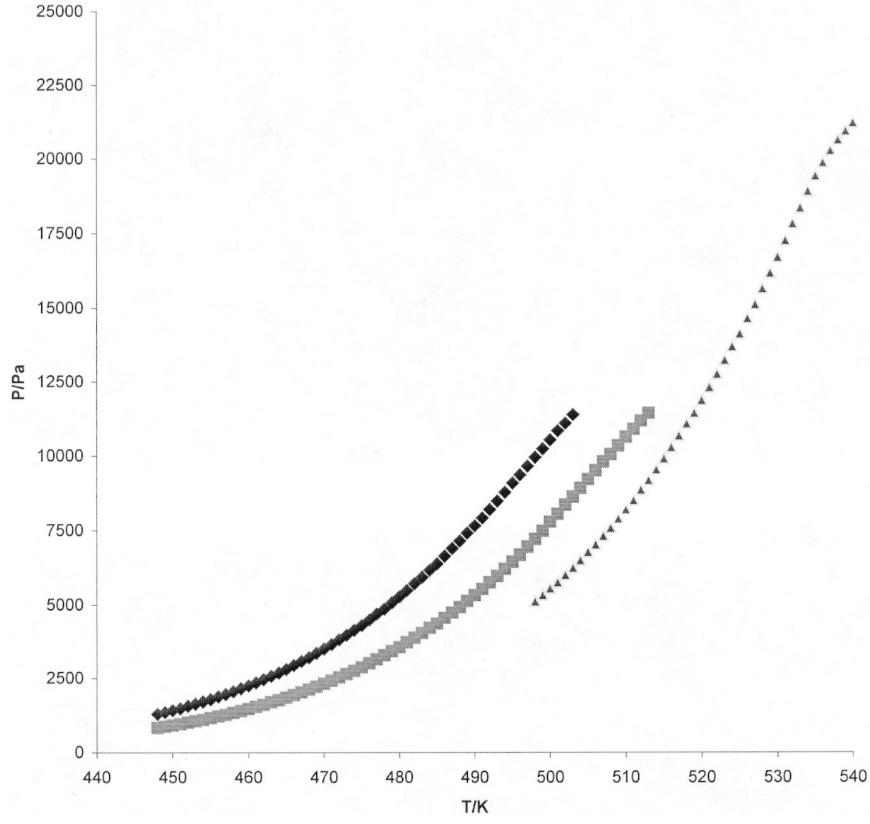

Fig. 5. Vapor-pressure plots for ethyl (◇), propyl (□), and butyl (△) parabens.

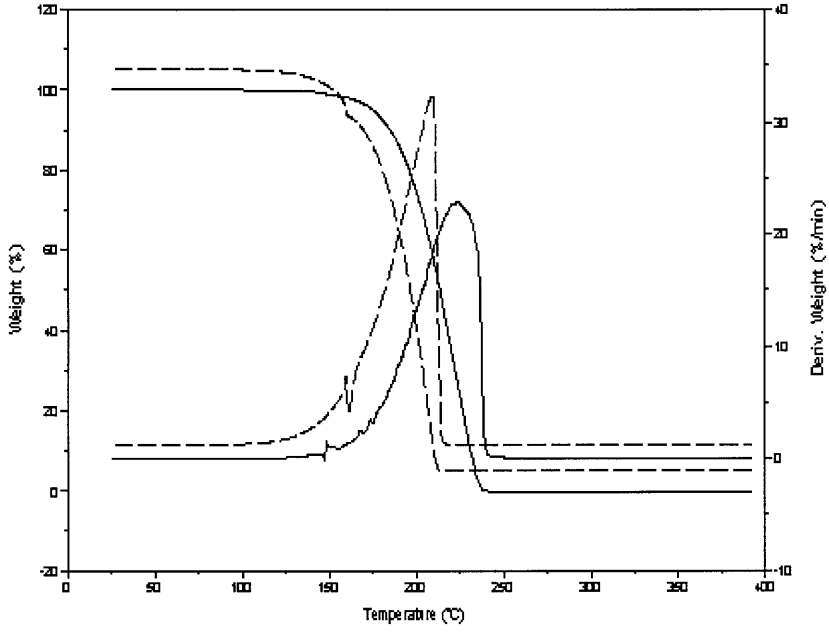

Fig. 6. TG-DTG curves for salicylic (---) and anthranilic (—) acid.

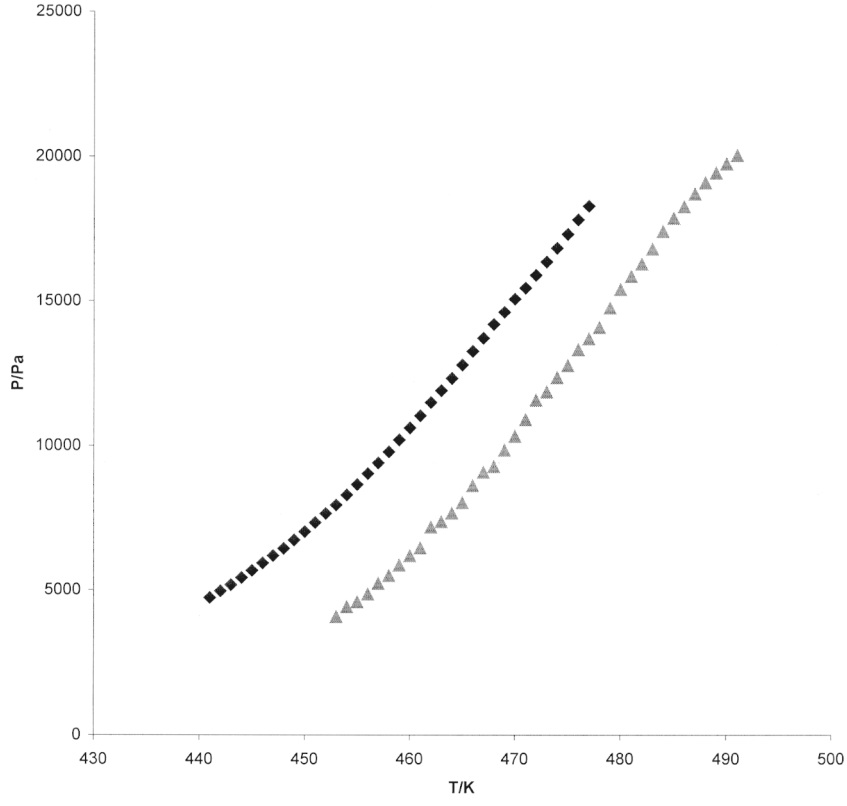

Fig. 7. Vapor-pressure plots for salicylic (◇) and anthranilic (△) acid.

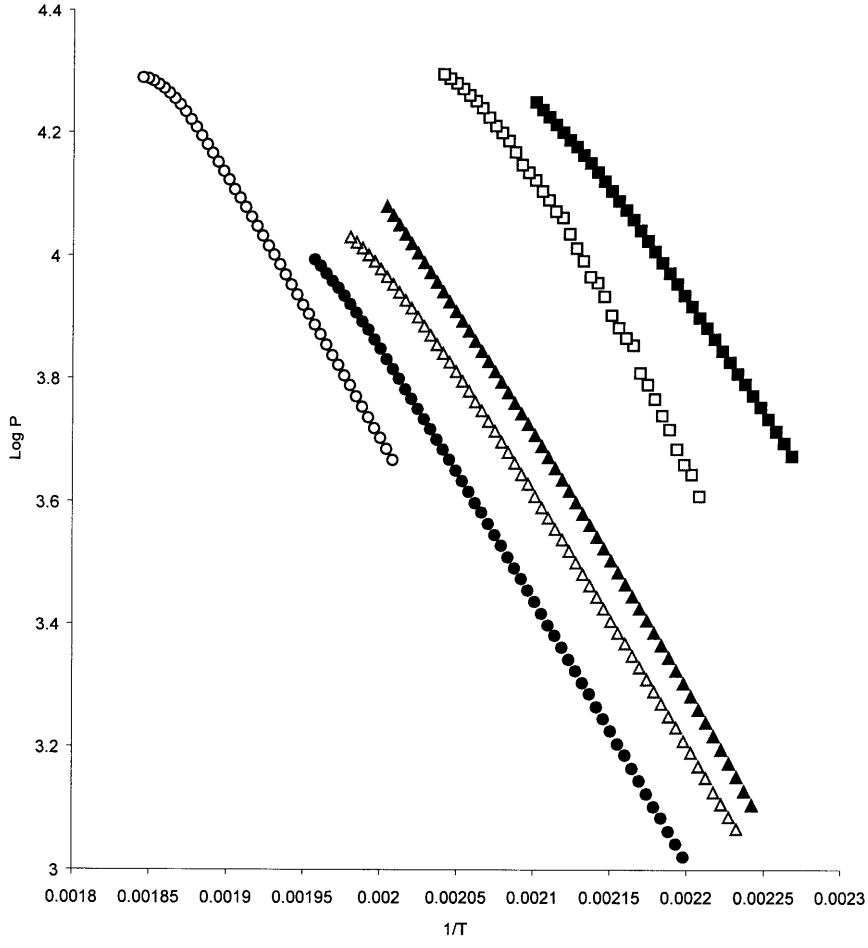

Fig. 8. Clausius–Clapeyron plots for methyl (▲), ethyl (△), propyl (●), butyl (○) parabens, salicylic (■), and anthranilic (□) acid.

Table 2
Antoine constants obtained by a non-linear regression least-square fit

Compound	Antoine constants			Temperature range (K)
	A	B	C	
Methyl paraben[a]	5.23	1159.34	−220.03	446–499
Ethyl paraben	7.32	794.37	−260.86	448–505
Propyl paraben	8.66	1491.58	−190.66	448–510
Butyl paraben	6.32	357.52	−363.96	498–542
Salicylic acid	6.28	316.74	−319.88	441–477
Anthranilic acid	5.36	97.22	−397.84	453–491

[a] Antoine constants reported in the literature.

pressure curve needed to define and quantify the vaporization characteristics. The process of actually measuring the vapor pressures has been not only time-consuming but also cumbersome, keeping in mind the classical manometric measurements. The method described in this study attempts to shorten the time span of such processes and offer comparable results. Another potential use for this method might be in the area of accelerated stability analyses of pharmaceuticals. Such analyses are inevitably used for reporting the stability of formulations at elevated temperature conditions. When such experiments are carried out, there exists an underlying assumption that all the components of the formulation remain unchanged at those elevated temperatures. Constructing vapor-pressure curves with the thermogravimetric data could be a useful tool to evaluate the evaporation of components at different temperatures. It might be argued that in the U.S.P., the temperature specified for accelerated thermal stability studies is lower than the temperature range used in this study. It is prudent to point out that the method adopted in this study is at its nascent stage and might require further refinements. Moreover, only single component systems have been studied, and future work must definitely attempt to characterize multi-component formulations. There remains a possibility that the melting point of a pure component might be depressed in the presence of other formulation additives. Once the vaporization (and sublimation, if any) characteristics of multi-component systems are validated by the method described in this study, the exact temperature for accelerated thermal stability can be corroborated for a particular formulation under study.

4. Conclusion

This work demonstrates that thermogravimetry is an effective technique for the determination of the coefficient of vaporization, when the Antoine vapor-pressure constants and the molecular weights of the substance in the vapor phase are known. Linear rising temperature conditions are very useful in obtaining a rapid means of measurement. For substances whose Antoine constants are not reported, a known substance can be effectively used to calibrate the procedure, and the vapor-pressure curve for that unknown substance can be plotted. The unknown Antoine constants can be obtained with proper curve-fitting procedures using least-square methods. There might be some disagreement regarding the value of (α), since, from this study, its value was found to be extremely small. However, this method can be effectively utilized as a rapid and reliable means of estimating the vaporization characteristics for pharmaceutical ingredients.

References

Aggarwal, P., Dollimore, D., Alexander, K.S., 1997. The Use of Thermogravimetry to follow the Rate of Evaporation of an ingredient used in Perfumes. J. Therm. Anal. 49, p595.

Annual Book of ASTM Standards, Designation: E 1719-97, 1997, Standard Test Method for Vapor pressure of Liquids by Ebulliometry, 11.01. West Conshohocken, Pennsylvania, USA.

Bardsley, W.G., Bukhari, N.A.J., Ferguson, M.W.J., Cachaza, J.A., Burguillo, F.J., 1995. Evaluation of model discrimination, parameter estimation and goodness of fit in nonlinear regression problems by test statistics distributions. Comput. Chem. 19 (2), 75–84.

de Kruif, C.G., Kuipers, T., Van Miltenburg, J.C., Schaake, R.C.F., Stevens, G., 1981. The vapor pressure of solid and liquid naphthalene. J. Chem. Thermodyn. 3, 1081.

Dollimore, D., O'Connell, C., 1998. A Comparison of Thermal Decomposition of Preservatives using thermogravimetry and rising temperature kinetics. Thermochim. Acta 324, 33.

Price, D.M.. Hawkins, M., 1998. Calorimetry of Two Disperse Dyes Using Thermogravimetry, 315, p. 19.

Elder, J.P., 1997. Sublimation measurements of pharmaceutical compounds by isothermal thermogravimetry. J. Thermal. Anal. 49, 897.

Goodrum, J.W., Siesel, E.M., 1996. Thermogravimetric analysis for boiling points and vapor pressure. J. Thermal Anal. 44, 1251.

Guckel, W., Kastel, R., Krohl, A., 1974. Parg. Pestic. Sci. 5, 393.

Haines, P.J., 1995. Thermal Methods of Analysis. Blackie Academic and Professional, London.

Langmuir, I., 1950, Phenomena, Atoms and Molecules. Philosophical Library, New York.

Majer, V., Svoboda, V., Pick, J., 1989. Heats of Vaporization of Fluids, Elsevier, Amsterdam, p.27.

McDowell, W., 1973. J. Soc. Dyers Colorists 895, 177.

Riberio da Silva, M.A.V., Monte, M.J.S., 1990. The construc-

tion, testing and use of a new Knudsen effusion apparatus. Thermochim. Acta 171, 169.

Shen, L., Alexander, K.S., 1999. A thermal analysis study of long chain fatty acids. Thermochim. Acta 340-341, 271–278.

Stephenson, R.M., Malamowski, S., 1987. Handbook of the Thermodynamics of Organic Compounds. Elsevier, New York, p. 263.

Wade, A., Weller, P.J., 1994, Handbook of Pharmaceutical Excipients, 2nd ed. The Pharmaceutical Press, London: 49, 191, 310 and 411.