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Sublimation and vapour pressure estimation of L-leucine using thermogravimetric analysis

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ABSTRACT

The sublimation kinetics of amino acid L-leucine is studied with the isothermal thermogravimetric (TG) analysis at temperatures between 400.7 and 517.5 K. Sublimation of L-leucine follows zero order kinetics. L-leucine begins to sublime around 423.2 K and sublimation rate increases exponentially with increasing temperature. The vapour pressure of L-leucine is determined based on the mass loss rate showing a good correlation with literature values. Using the Arrhenius equation, the activation energy and pre-exponential factor are determined. The sublimation enthalpy and entropy are obtained using the Clausius–Clapeyron equation.

1. Introduction

Amino acid L-leucine is an effective excipient that improves the properties of powders such as dispersibility, flowability and stability [1–4]. Surface accumulation of L-leucine on drug particle surfaces has been achieved by powder blending [3,4], surface-diffusion in spray-drying [5,6] and physical vapour deposition (PVD) [7]. Among these techniques, the PVD method enables to efficiently tailor the characteristics of an L-leucine coating layer that affects significantly the properties of coated particles [2,8]. However, understanding the formation of the coating layer to optimise powder properties requires good control over vapour pressure and sublimation of L-leucine.

Thermodynamic properties of amino acids have been studied extensively [9,10]. These studies focused more on thermal stability and less attention was paid to vapourisation kinetics. The vapour pressure of L-leucine has been previously reported using various techniques. It is known that thermal transitions of a material may rely on the equipment used and on the experimental set-up. For instance, Svec and Clyde used an effusion method at a narrow temperature range [11] and obtained approximately 270 times lower vapour pressure of L-leucine than Gaffney et al. [12] who used mass spectrometer. Differential scanning calorimetry (DSC) measurements performed by Li et al. [13] showed that L-leucine sublimed at 567.2 K followed by decomposition at 576.2 K. Martins et al. [14] found that L-leucine sublimed at 524.2 K when measured by DSC whereas the sublimation took place at 563.2 K when using thermogravimetric analysis (TGA). On the other hand, it has been also reported that L-leucine sublimes at distinctly lower temperatures of 418.2–421.2 K [15]. Likewise, we observed in our previous work that the sublimation of L-leucine from nanoparticles in the gas phase initiated markedly below 473.2 K [7]. Such diverse results indicate that the sublimation kinetics of L-leucine is not thoroughly understood and more precise and reliable measuring methods are required.

Thermogravimetric analysis is typically used to study the characteristics of materials such as degradation, absorbed moisture content and solvent residues. In addition, it can be used for the study of phase transitions such as sublimation and related properties such as vapour pressure [16]. In comparison to the methods where the vapour pressure is measured directly in a saturated gas atmosphere, TGA provides a fast and reliable procedure to study a number of compounds that are thermally stable up to their melting point at ambient pressure [16,17]. It is a very sensitive method and allows good control over the gas and sample surface temperatures [16,18] providing an accurate measurement of the sample loss rate. Using this method, the evaporation rate of a compound determined under isothermal conditions is directly related to the vapour pressure of the material [16,17].

In the present study, the sublimation kinetics of L-leucine was studied by TGA under isothermal conditions. Activation

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energy, pre-exponential factor and the heat of sublimation of L-leucine were determined using Arrhenius and Clausius–Clapeyron equations.

2. Materials and methods

2.1. Materials

Commercially available, crystalline L-leucine (PhEur grade, Fluka, Switzerland) was used without further purification. Anhydrous caffeine (SigmaUltra, Sigma–Aldrich, Germany) was used as a calibration substance without further purification.

2.2. Methods

2.2.1. Measurements

All mass loss determinations were carried out using a Netzsch STA 449C (Netzsch-Gerätebau GmbH, Germany) thermobalance. A highly sensitive microbalance used in TGA provides an accurate estimate of vapour pressure even at atmospheric environment when measuring the sublimation rate. The measurements were carried out in dynamic nitrogen atmosphere with a flow rate of 40 ml/min. In all cases the amount of sample was kept low (approximately 3 mg placed in an open 85 μl alumina crucible) in order to minimise thermal gradients but to fully cover the bottom of the crucible. Data acquisition and analysis were done using Netzsch Proteus software for thermal analysis (Netzsch-Gerätebau GmbH, Germany).

The experiments were conducted at a temperature range from 369.5 to 517.5 K (±0.01 K) under isothermal conditions. The furnace temperature was programmed to rise linearly with the rate of 40 K/min from ambient to target temperature and then maintaining this temperature. Mass loss rates (dm/dt) were determined from a region where the temperature was constant and mass loss was at least 20%.

2.2.2. Equipment calibration

The mass loss rate of a substance is related to its vapour pressure and can be expressed by the Langmuir equation

$$P = \frac{\sqrt{2\pi R}}{\alpha} \times \frac{dm}{dt} \times \sqrt{\frac{T}{M}} \quad (1)$$

where P is the vapour pressure, R is the universal gas constant, α is the vapourisation coefficient, dm/dt is the rate of mass loss with respect to time, T is the absolute temperature and M is the molecular weight of the substance in the vapour phase. This equation is applicable in the vacuum conditions where α is unity. In the present thermogravimetric studies, however, the measurements were performed in dynamic nitrogen atmosphere in approximately atmospheric pressure when α was no longer unity. This problem can be overcome by using a calibration substance with a known vapour pressure. In this study, the calibration substance was caffeine that vapourises approximately in the same temperature range as L-leucine.

The vapourisation rate of caffeine was determined between 369.5 and 496.7 K using the same experimental configuration as with L-leucine. The mass loss rate was plotted against the vapour pressure given in literature [19] at temperatures between 418.2 and 496.7 K, since the mass loss rate of caffeine was very slow below 418.2 K. The following linear logarithmic relationship between vapour pressure and mass loss rate [16,18] is determined as follows:

$$\ln P = a \times \ln\left(\frac{dm}{dt}\right) + b \quad (2)$$

where P is the vapour pressure at a given temperature, dm/dt is the rate of sublimation, a and b are constants specific for the instrument and for the experimental procedures as described above. The values of a and b were 1.374 and 0.397, respectively, as estimated from the plot with $R^2 = 0.99$. One should note that the linear relationship between sublimation rate and vapour pressure is independent of material and the temperature range used but it depends on experimental features like the equipment and its configuration and the design of the sample crucible [18,20].

According to Focke [21], however, the vapourisation rate measured with TG is influenced by gas phase diffusion coefficient of the compound (D_{ab}). In the case of mass transport limited by diffusion through a stagnant medium (e.g. inert gas) the vapour pressure of the compound can be determined using the calibration compound with known vapour pressure while taking the diffusion coefficients into account as follows:

$$P_s = P_r \left(\frac{D_{rb}}{D_{sb}}\right)\left(\frac{M_r}{M_s}\right)\left(\frac{(dm/dt)_s}{(dm/dt)_r}\right) \quad (3)$$

where P is the vapour pressure, D is the diffusion coefficient, M is the molecular weight and dm/dt is the mass loss rate of compounds s and r to the gas phase.

The diffusion coefficient of the vapour was estimated using the equation derived from literature [22]:

$$D_{ab} = \frac{2}{3nd_c^2}\sqrt{\frac{RT}{\pi^3 M}} \quad (4)$$

where n is the number of vapour molecules taken to be the same as the number of gas molecules in air (2.5×10^{25} 1/m^3) and d_c is the collision diameter of the molecule that is considered to be the same as the diameter of the molecule that is 7.4 Å for caffeine [23] and 6.8 Å for L-leucine [24].

3. Results and discussion

Fig. 1 shows the thermograms of mass loss with time at temperatures from 400.7 to 517.5 K. As seen, the mass of L-leucine decreased linearly implying a zero order evaporation process [25]. Table 1 summarizes the mass loss rates of L-leucine at different temperatures and corresponding vapour pressures. At 400.7 K no sublimation of L-leucine was detected. At 420.7 K the sublimation rate was 0.3 μg/min and it increased exponentially with increasing temperature being 65.2 μg/min at 517.5 K.

Table 1 shows the vapour pressures of L-leucine (P_{LE}) calculated with the Eqs. (2) and (3). The vapour pressure values obtained with

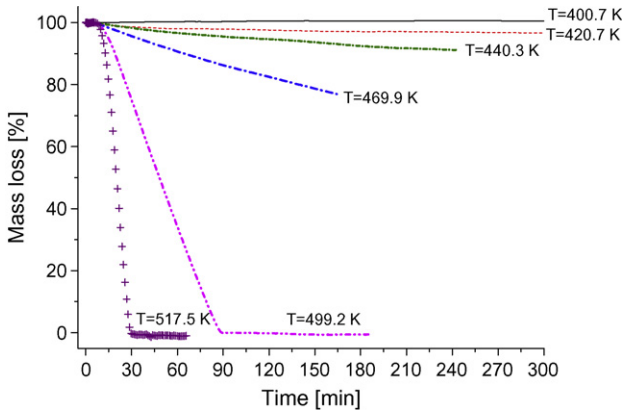


Fig. 1. The thermograms of L-leucine from 400.7 to 517.7 K showing the weight loss under isothermal conditions.

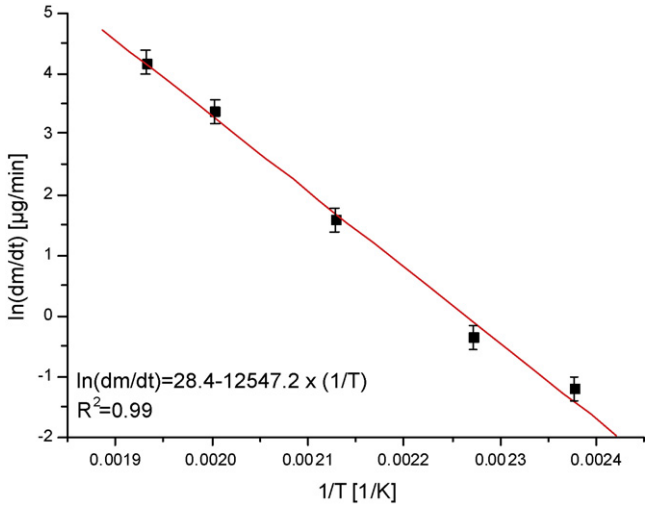
Table 1
Mass loss rate and vapour pressure of L-leucine powders derived from TGA measurements. Vapour pressure derived from Svec and Clyde [11]. P^2_{LE} is determined with Eq. (2) and P^3_{LE} with Eq. (3).

Temperature (K)	dm/dt (μg/min)	P^2_{LE} (Pa)	P^3_{LE} (Pa)	P_{LIT} (Pa) [11]	P^3_{LE}/P_{LIT}
400.7	0	–	–	0.06	–
420.7	0.3	0.3	0.9	0.5	1.8
440.3	0.7	0.9	2.9	2.9	1.0
469.9	4.9	13.2	42.5	46.9	0.9
499.2	29.3	154.6	526.3	450.2	1.2
517.5	65.2	464.26	2162.3	1624.1	1.3

the Eq. (3) (P^3_{LE}) were highly parallel with the values given in literature [11], see Fig. 2, while vapour pressures calculated with Eq. (2) (P^2_{LE}) were significantly lower. The results show that the determination of vapour pressure of a compound requires the knowledge of the compound diffusion coefficients as stated by Focke [21].

The sublimation kinetics of L-leucine were estimated using Arrhenius equation

$$\ln\frac{dm}{dt} = \ln A - \frac{E_a}{RT} \quad (5)$$



where dm/dt is the reaction rate constant, A is the pre-exponential factor, E_a is the activation energy, R is the universal gas constant and T is the absolute temperature in Kelvins. The Arrhenius parameters of L-leucine were determined from the plot where the activation energy was deduced from the slope and the pre-exponential factor from the intercept value. From the plot (R^2 = 0.99), the activation energy (E_a) and pre-exponential factor (ln$A$) of L-leucine were 104.4 ± 4.0 kJ/mol and 28.4 ± 1.0, respectively.

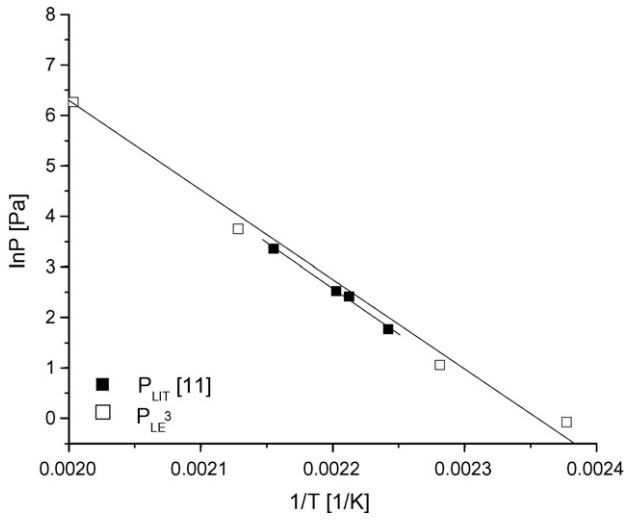
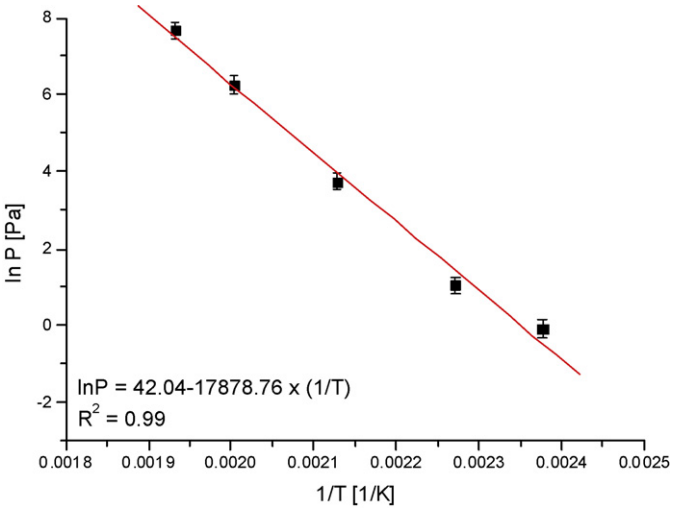


Fig. 2. The comparison of vapour pressures obtained in this study (P^3_{LE}) and values derived from the literature (P_{LIT}) [11].

Under normal pressure, the gas phase diffusion of molecules can be assumed to be the rate limiting step. Accordingly, at the gas–solid interface the desorption and adsorption of molecules are at equilibrium and the vapour pressure of a substance is equal to the saturation vapour pressure by the Clausius–Clapeyron equation

$$\ln P = -\frac{\Delta H}{R}\left(\frac{1}{T}\right) + \frac{\Delta S}{R} \quad (6)$$



where T is temperature in Kelvins, ΔH is the standard enthalpy change of sublimation process, R is the molar gas constant and ΔS is the standard entropy of sublimation. L-leucine sublimes from solid to vapour directly without decomposition [14] in the temperature range used in this study. The vapour pressure of L-leucine calculated with Eq. (3) was used in the Eq. (6). From the graph ln$P$ vs. 1/T (R^2 = 0.99), the enthalpy of sublimation was 148.7 ± 6.5 kJ/mol and entropy 349.5 ± 13.4 J/mol K.

Table 2 summarizes the physical parameters of L-leucine in comparison to those reported in literature. One can note that the previously reported E_a was 20–25 % higher and ΔS around 27% lower than those determined in this study [9–11,13]. ΔH value was in close agreement with the value reported by Svec and Clyde [11] but deviated from value measured with TG–DSC about 18% [10]. These deviations can be explained as follows. Rodante et al. [9,10]

Table 2
The physical parameters of L-leucine determined with isothermal (IT) thermogravimetric measurements between 400.7 and 517.7 K compared to the literature values.

	This study	Literature				
		Values	T range (K)	Condition	Method	Ref.
E_a (kJ/mol)	104.4 ± 4.0	130.0	293–615	Non-IT	TG–DSC	[9]
		134.8	293–615	Non-IT	TG–DSC	[10]
		138.0	293–873	Non-IT	TG–DSC	[13]
ln$A$	28.4 ± 1.0	26.3	293–615	Non-IT	TG–DSC	[9]
		27.4	293–615	Non-IT	TG–DSC	[10]
		23.8	293–873	Non-IT	TG–DSC	[13]
ΔH (kJ/mol)	148.7 ± 6.5	150.6	455[a]	IT	Effusion	[11]
		121.3	293–615	Non-IT	TG–DSC	[10]
ΔS (J/mol K)	349.5 ± 13.4	256.7	455[a]	IT	Effusion	[11]

[a] Measured temperature range 446–464 K.

assumed that the sublimation of L-leucine followed first order reaction kinetics. However, it has been shown in this study and by Li et al. [13] that the sublimation of L-leucine is actually a zero order process. Moreover, in the measurements that were carried out under non-isothermal conditions (dynamic TG–DSC), the Arrhenius parameters were determined using an integral expression of kinetic model function that has no analytical solution and approximation formula was used.

4. Conclusions

The sublimation kinetics of L-leucine was studied with thermogravimetric measurements under isothermal, dynamic conditions at wide temperature range. A clear evidence for the sublimation of L-leucine was observed at 420.7 K as a gradual mass loss with time. The sublimation rate increased exponentially with elevated temperature being more than 200 times higher at 517.5 K. The mass loss rate followed zero order kinetics. Arrhenius parameters, enthalpy and entropy of sublimation deviated markedly from non-isothermal measurements. Isothermal TG analysis provides a simple way for the determination of thermodynamic and kinetic data of low volatility compounds.

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