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# Implementation and validation of the thermogravimetric method for the determination of equilibrium vapour pressure values and sublimation enthalpies of frozen organic formulations used in drug freeze–drying processes

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## A B S T R A C T

The modelling of the sublimation step needs the knowledge of basic thermodynamic properties as the equilibrium solid–vapour pressures and the sublimation enthalpies. Unfortunately these thermodynamic properties are generally missing in the literature.

Tert-butanol (TBA) co-solvent has been used largely as solvent in freeze–drying formulation.

Thus, in the present study, we have determined the equilibrium values of vapour pressures (solid–vapour and liquid–vapour equilibrium) and sublimation enthalpies of pure TBA and for its eutectic mixture with water, namely the 90% (w/w) TBA + 10% (w/w) mixture, by using two different and comparative methods: the Thermogravimetric Method (TG Method) and the Static Method.

TG experiments were conducted in dynamic conditions in a temperature range from  $-30^{\circ}\text{C}$  to  $80^{\circ}\text{C}$ . Both methods led to similar values with a relative deviation less than 2%.

This validation proved that the TG method is a rapid, reliable and precise technique for the determination of solid/vapour and liquid/vapour equilibrium pressures for pure substances or for co-solvent + water mixtures at eutectic/azeotropic compositions.

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## 1. Introduction

Freeze–drying or lyophilization is the process by which the solvent is removed from a frozen solution by sublimation (Pikal, 2002). The freeze–drying process may be divided into three steps: freezing, primary drying (or sublimation) and secondary drying (or desorption). A large majority of pharmaceutical products are lyophilized with simple aqueous solutions. In this case, water is typically the only solvent present which is removed from the solid phase firstly by sublimation and next by desorption.

However, some hydrophobic and insoluble active principle ingredient (API) can be freeze-dried from pure organic

solvent or organic co-solvent formulations. The organic solvent that has been most extensively evaluated seems to be pure tert-butanol or TBA mixtures where it is diluted in water (Teagarden and Baker, 2001; Rey and May, 2004; Daoussi et al., 2009, 2011).

The main advantages of using this non aqueous solvent are the following: increased drug wetting or solubility, increased solution and dried product stability, lower reconstitution times and principally very high sublimation rates leading to very short sublimation times. In our laboratory, Daoussi (2008) lyophilized a commercial API by using different TBA + water mixtures in the range from 80% (w/w) TBA to 100% pure TBA, and for many different operating conditions (temperature, total pressure).

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We observed that the use of organic co-solvent, especially the eutectic 90% (w/w) TBA + 10% (w/w) water mixture, reduced considerably the sublimation times around 2 h 30, these values being 10–11 times lower than the values observed with pure aqueous solvent formulations under the same operating conditions of sublimation.

Furthermore, the fine physical modelling of the sublimation step needs the precise knowledge of some thermodynamic properties like solid–vapour equilibrium pressures and sublimation enthalpies for pure TBA and for the 90% (w/w) TBA + 10% (w/w) water system.

This is why the present study reports the values of these determinations by using two different and comparative methods: the Thermogravimetric Method (called TG method) and the direct Static Method used as validation method.

## 2. Methods and materials

### 2.1. Thermogravimetric Method

Over the years, the determination of equilibrium vapour pressures data of volatile organic substances by using the TG method has been reported by numerous authors (Phang et al., 2002; Chatterjee et al., 2002; Surov, 2009). The implementation of this method was based on the application of the Langmuir equation for free evaporation from solid–vapour or from liquid–vapour interfaces (Langmuir, 1913). This equation expresses as follows:

$$\left(\frac{1}{a}\right) \frac{dm}{dt} = P\alpha \sqrt{\frac{M}{2\pi RT}} \quad (1)$$

where  $(1/a)(dm/dt)$  represents the rate of mass loss per unit area ( $\text{kg s}^{-1} \text{m}^{-2}$ ),  $P$  the equilibrium vapour pressure (Pa),  $M$  the molecular weight of the evaporating compound ( $\text{kg mol}^{-1}$ ),  $R$  the universal gas constant ( $\text{J K}^{-1} \text{mol}^{-1}$ ),  $T$  the absolute temperature (K) and  $\alpha$  the vaporization coefficient. In vacuum conditions,  $\alpha$  is assumed to be equal to 1, but with flowing gas atmosphere, as commonly found in TG experiments,  $\alpha$  value can be significantly different. Thus, Price (2000) validated a rigorous procedure to estimate the equilibrium vapour pressure of liquid or solid substances, from thermogravimetric data obtained in the presence of an inert purge gas at atmospheric pressure. The interpretation of his experimental data was based on Langmuir relationship (Eq. (1)) rewritten in the following form:

$$P = k\nu \quad (2)$$

where the term  $\nu = (1/a)(dm/dt)\sqrt{T/M}$  and  $k = \sqrt{2\pi R}/\alpha$  represents the calibration constant.

The TG method consists to determine the rate of mass loss over the temperature range of interest by using a reference substance thermally stable with known precise vapour pressure values. The vapour pressure values of pure substance as the reference compound can be correlated by using the Antoine equation of the form:

$$\ln P = A - \frac{B}{C + T} \quad (3)$$

where  $A$ ,  $B$ , and  $C$  represent empirical constants,  $P$  the vapour pressure in Pa and  $T$  is the absolute temperature. Pretty frequently, benzoic acid was chosen as reference substance in

TG experiments (Wright et al., 2004). Then, a plot of  $P$  (equilibrium reference compound vapour pressure) as a function of variable  $\nu$  (calculated from experimental TG data) should give a straight line with a slope equal to the calibration constant, noted  $k$ . Next, this calibration constant can be used to calculate the equilibrium vapour pressure values for any compound for which the Antoine constants are unknown. It should be observed that the  $k$  value is often assumed to be independent of experimental conditions (temperature, pressure, flow rate). One fundamental assumption of (Eq. (2)), is that the vaporization coefficient,  $\alpha$ , keeps a constant value close to unity. However, in practice, it was observed, that the value of  $\alpha$  deviated significantly from unity for experiments conducted in the presence of purge gases.

In order to overcome this difficulty called “non ideal” vaporization, Phang et al. (2002) proposed a comparative method based on basic Langmuir relationship (Eq. (1)). This method consists in combining the evaporation data obtained by thermogravimetry (TG) of the investigated sample (S) with the equilibrium vapour pressure data of a suitable reference product (R). The Langmuir equations for this reference product and for the sample under investigation can be written as follows:

$$\left(\frac{dm}{dt}\right)_R T^{1/2} = \alpha M_R^{1/2} \left[\frac{1}{2\pi R}\right]^{1/2} P_R \quad (4)$$

$$\left(\frac{dm}{dt}\right)_S T^{1/2} = \alpha M_S^{1/2} \left[\frac{1}{2\pi R}\right]^{1/2} P_S \quad (5)$$

Thus, the ratio of Eqs. (4) and (5), after rearrangement of the resulting relation in terms of  $P_S$  leads to the following relationship:

$$P_S = \left(\frac{M_R}{M_S}\right)^{1/2} P_R \left[\frac{(dm/dt)_S}{(dm/dt)_R}\right] \quad (6)$$

from which the terms  $T^{1/2}$ ,  $\alpha$  and  $[1/2\pi R]^{1/2}$  are eliminated.

Nevertheless, for a reliable and precise application of this method, it is necessary that the two components (R) and (S) present structural molecular similarities and that they evaporate within a similar temperature range.

Moreover, Focke (2003) proposed a slightly modified version of Eq. (6) as follows:

$$P_S = \left(\frac{D_R}{D_S}\right) \left(\frac{M_R}{M_S}\right) P_R \left[\frac{(dm/dt)_S}{(dm/dt)_R}\right] \quad (7)$$

where  $D_R$  and  $D_S$  refer to the reference and to the investigated product diffusion coefficients through the flowing inert gas. These diffusion coefficients values can be estimated by using Fuller’s method (Millat et al., 1996) based on the following relationship:

$$D_{AB} = \frac{0.00143T^{7/4}}{P(M_{AB})^{1/2}[(\sum \nu)_A^{1/3} + (\sum \nu)_B^{1/3}]^2} \quad (8)$$

where  $D_{AB}$  ( $\text{cm}^2/\text{s}$ ) represents the diffusivity of the component  $A$  in the inert gas  $B$  (nitrogen),  $T$  the temperature in Kelvin,  $P$  the total gas pressure in bar, the molecular weight term  $M_{AB} = (M_A M_B)/(M_A + M_B)$  in  $\text{g mol}^{-1}$ , and the term  $(\sum \nu)_A^{1/3} + (\sum \nu)_B^{1/3}$  represents an empirical correction factor expressed as a function of atomic volume increments of each component noted  $\nu$  (Millat et al., 1996). Furthermore, the temperature

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