Thermochimica Acta 493 (2009) 37–41

Contents lists available at ScienceDirect

Thermochimica Acta

journal homepage: www.elsevier.com/locate/tca

Isothermal microcalorimetry perfusion experiments: A method to verify the relative vapour pressure of organic liquids inside the sample vessel

Julia Baronsky[a,b,*], Sabine Bongaerts[b], Michael Traeubel[b], Nora Urbanetz[a]

[a] *Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Duesseldorf, Germany*
[b] *BAH-RD-A, Bayer Animal Health GmbH, Leverkusen, Germany*

ARTICLE INFO

Article history:
Received 30 October 2008
Received in revised form 27 March 2009
Accepted 1 April 2009
Available online 10 April 2009

Keywords:
Isothermal microcalorimetry
Relative vapour pressure
Perfusion
Vapour sorption

ABSTRACT

Perfusion microcalorimetry is frequently applied to expose pharmaceutical solids to specific relative vapour pressures (RVP) of organic liquids or water. The aim was to set up a general procedure to check the performance of a vapour pressure control device used to create a specific RVP. This was achieved by identifying and checking the significant factors in the creation of the RVP inside the reaction vessel. The flow switch valve was tested by volume flow measurements whereas the saturation of the wet line was verified in a calorimetric experiment employing methanol as model solvent. The results of the measurements were used to calculate the RVP inside the reaction vessel. The method developed is suitable to test the vapour pressure control device. It can be applied for any solvent.

1. Introduction

In pharmaceutical sciences, the interaction of pharmaceutical solids with both water vapour and organic vapours plays an important role. Vapours may affect the physical and chemical properties of both active ingredients and excipients [1]. Additionally, the interaction with vapours is used as an analytical tool to determine low amounts of amorphous material in a crystalline substance or to investigate powder surface properties, for example [2,3]. A possibility to monitor the interaction is isothermal microcalorimetry (IMC). IMC measures the heat flow as a function of time. As the interaction of sample and vapours itself as well as each process which may result from the interaction absorbs or produces heat, IMC is a suitable method to record the heat flow of the interaction and of possible following reactions.

There are two ways of exposing the sample to a specific relative vapour pressure (RVP) while measuring thermal activity. One possibility is to place a small glass tube inside the sample vessel [4]. The tube is filled either with a saturated aqueous salt solution [5–7] or with organic solvents or mixtures of solvents [8,9] in order to create a certain RVP of water or organic solvent inside the sample ampoule. The "miniature humidity chamber" method has been used to assess low amounts of amorphous content in crystalline powders as well as to study the process of crystallisation of various amorphous substances [10–12]. It is a simple and inexpensive technique but has several disadvantages. For example, a controlled change of RVP within an experiment is not possible.

The alternative way of exposing the sample to a specific RVP is the use of a perfusion system [13]. In a special perfusion ampoule, a carrier gas with a predefined RVP flows over the sample. The RVP can be altered stepwise or continuously during the experiment. The vapour pressure control device is mainly used to control relative humidity (RH). RH perfusion microcalorimetry has a wide range of applications including the assessment of powder surface energies, the formation of hydrates, the onset of deliquescence and the study of amorphous material [2,14–17].

The design of the perfusion system also allows the control of the RVP of organic solvents [18]. In several cases, amorphous hydrophobic powders do not crystallise in the presence of water vapour at experimental temperature, however, they may crystallise in the presence of a specific RVP of an organic solvent [19]. Consequently, perfusion microcalorimetry enables the quantification of low amounts of amorphous material in hydrophobic substances [20]. Furthermore, polymorphic substances that undergo phase transformation in the presence of organic vapours can be characterised.

In order to reliably perform perfusion calorimetry, it is important to verify the performance of the vapour pressure control device. If the perfusion system is used to create a specific RH, the generation of the predefined RH inside the sample vessel can be checked with the help of saturated aqueous salt solutions [21]. Saturated salt solutions maintain a constant RH at a certain temperature. Placing a saturated salt solution inside the sample vessel of the RH perfusion

---

* Corresponding author at: BAH-RD-A, Bayer Animal Health GmbH, Building 6820, 51368 Leverkusen, Germany. Tel.: +49 21 73 38 46 80; fax: +49 21 73 38 30 27.
E-mail address: julia.baronsky@gmx.net (J. Baronsky).

0040-6031/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.tca.2009.04.001

ampoule, the heat flow will become zero if the RH of the gas flowing over the solution corresponds to the RH of the salt solution.

To our knowledge, a comparable method to ascertain the RVP of organic solvents has not been reported yet. The aim of this work is to develop a general procedure to determine the RVP inside the reaction vessel of the RH perfusion ampoule (RVP_{in}). To do so, the essential steps in the generation of the RVP have to be identified. The vapour pressure control device creates the designated RVP by mixing dry carrier gas with gas saturated with vapours of the respective solvent. The flow rates of the two gas lines are either controlled by two mass flow controllers [22], two peristaltic pumps [23] or by a flow switch valve. Consequently, the regulation of the two flow rates is one significant element in the generation of the RVP. In addition, the saturation of one of the gas lines with vapours of the organic solvent used plays an important role.

In this work, these two fundamental points are checked as a general approach to assess the RVP created by the vapour pressure control device.

2. Experimental

2.1. Materials

Methanol for analysis was obtained from Merck, Darmstadt, Germany. Purity was 99.9% or higher.

2.2. Isothermal microcalorimetry

The vapour pressure control device tested is designed for the 2277 Thermal Activity Monitor (formerly Thermometric AB, Järfälla, Sweden, now TA Instruments, New Castle, USA). It consists of the 2250-010 RH Perfusion Ampoule (TA Instruments, New Castle, USA) combined with a flow control system. The flow control system is composed of a mass flow controller (Bronkhorst High-Tech, AK Ruurlo, Netherlands), a flow switch valve (TA Instruments, New Castle, USA) and the 2281 Flow Switch Module (TA Instruments, New Castle, USA).

The mass flow controller adjusts the flow of dry nitrogen being delivered to the flow switch valve. The flow rate was set to 50 ml/h (0 °C, 1.01325 bar). The actual flow of nitrogen measured using a soap film meter (see Section 2.3) was 52.7 ± 0.27 ml/h (standard deviation, $n = 3$) (0 °C, 1.01325 bar). The nitrogen flow is divided into two lines by the flow switch valve (Fig. 1). One line leads directly to the reaction vessel (dry line). The other line passes two solvent reservoirs in order to be saturated with solvent vapours before entering the reaction vessel (wet line). The RVP inside the reaction vessel is created by the ratio of the time interval the dry line is open (0% RVP) to the time period the wet line is open (100% RVP). By predefining a specific RVP (RVP_{set}) in the Digitam® software (TA Instruments, New Castle, USA) used for operating TAM, the ratio of the switching times in a switching cycle is set. The switching cycle time is the time period within the valve switches once. It was set to 10 s. The heater placed close to the flow switch valve was set 20 °C above the temperature of TAM.

The calorimetric experiment to check the saturation of the wet line was performed at 25 °C. An empty, closed stainless steel ampoule was taken as reference ampoule. 0.5 ml methanol was filled in each solvent reservoir of the RH perfusion ampoule. 0.8 ml methanol was directly inserted into the reaction vessel. The perfusion unit was placed into the measuring position of the TAM after a thermal equilibration period of 20 min in the different equilibration positions. Heat flow measurement was started. The RVP was first set to 80% for 2 h. Then, RVP_{set} was increased in 5% steps up to 95%. 100% RVP_{set} was not used in the experiment in order to avoid possible condensation. Time delay of each step was 2 h. The calorimetric experiment was performed three times. Additionally, the baseline heat flow of the empty reaction vessel was determined at the different RVP_{set} values. Prior to the start of the measurements, the calorimeter was calibrated using a static calibration. The calibration heat flow generated by the internal calibration heater resistors was 3000 μW. The calibration was performed having the perfusion ampoule inside the measuring position and the reference ampoule inside the reference position. During calibration, the solvent reservoirs and the reaction vessel of the perfusion ampoule were empty and the gas flow was turned off.

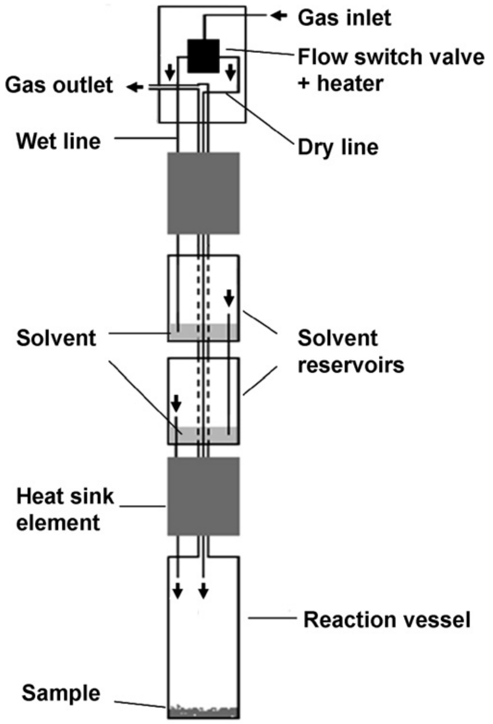

Fig. 1. Schematic drawing of the RH perfusion ampoule and the flow switch valve.

2.3. Volume flow measurements

The volume flow rates of the wet line and the dry line were measured in order to verify the accuracy of the operation of the flow switch valve. Measurements were performed using a 10 ml soap film flow meter (Agilent Technologies, Santa Clara, USA). The flow meter is a glass tube scaled in 0.05 ml units. After having wetted the inside of the meter with a soap solution, gas is passed through. The formed soap film being pushed up by the incoming gas enables the measurement of the increase in volume in a certain time period.

In order to carry out the volume flow measurements, the RH perfusion ampoule was placed outside the microcalorimeter. The solvent reservoirs were emptied and the heater was turned off. The reaction vessel was removed giving the possibility of connecting either the dry line or the wet line to the soap film flow meter. For each RVP tested, a new calorimetric experiment was started in the Digitam® software. The flow rate of nitrogen applied was the same as described in Section 2.2. The RVP_{set} values tested were 0, 20, 40, 60, 80, 85, 90, 95 and 100%. For each RVP, the volume leaving the wet and the dry line, respectively, within a period of 10 min was measured. Each measurement was repeated twice. At the beginning of each measurement, ambient temperature and pressure were recorded.

Table 1
Volume flow rates of the wet and the dry line and the RVP_{valve} values calculated from the volume flow rates at different RVP_{set} values.

RVP_{set} (%)	f_{dry}[a] (ml/h)	f_{wet}[a] (ml/h)	RVP_{valve}[b] (%)
0	52.9 ± 0.72	–	0
20	42.4 ± 0.16	10.9 ± 0.10	20.4 ± 0.06
40	32.0 ± 0.24	21.1 ± 0.20	39.8 ± 0.18
60	21.6 ± 0.17	31.7 ± 0.18	59.4 ± 0.12
80	11.2 ± 0.02	42.0 ± 0.21	78.9 ± 0.05
85	8.4 ± 0.02	44.7 ± 0.12	84.2 ± 0.03
90	6.1 ± 0.09	47.0 ± 0.21	88.6 ± 0.06
95	3.4 ± 0.03	49.7 ± 0.22	93.6 ± 0.01
100	–	52.2 ± 0.42	100

[a] Volume flow rate at 0 °C, 1.01325 bar. Mean value out of three identical measurements ($n = 3$) ± standard deviation.

[b] RVP_{valve} = ratio of f_{wet} to the sum of the flow rates coming out of the wet line and the dry line at RVP_{set} ($f_{wet} + f_{dry}$), multiplied by 100%. For each RVP_{valve} (except 0 and 100%), the standard error according to the Gaussian error propagation is given.

3. Results

3.1. Testing of the flow switch valve

Throughout the measurements, the temperature ranged from 21.7 to 22.0 °C. Atmospheric pressure varied between 1.006 and 1.016 bar. Because of these fluctuations, the measured flow rates were normalised to standard conditions (0 °C and 1.01325 bar). The converted flow rates are listed in Table 1 (mean value ($n = 3$) ± standard deviation).

The mean values of the flow rates of the dry and wet line, f_{dry} and f_{wet}, were used to calculate RVP_{valve} as a term providing information about the accuracy of the valve:

$$RVP_{valve} = \frac{f_{wet}}{f_{wet} + f_{dry}} \times 100\% \qquad (1)$$

RVP_{valve} is the ratio of f_{wet} to the sum of the flow rates coming out of the wet and the dry line, multiplied by 100%. It represents the fraction of the gas directed to the wet line. If the valve works accurately, the fraction of the gas passing through the wet line equals the value of RVP_{set}. Consequently, RVP_{valve} describes the actual RVP provided by the flow switch valve. The RVP_{valve} values for the different RVP_{set} values tested are displayed in Table 1. The table shows that the absolute deviation of RVP_{valve} from RVP_{set} is low within the whole RVP range. The highest absolute deviation is found at 90 and 95% RVP_{set} being 1.4%. However, taking RVP_{valve} ± twice the standard error as the 95% confidence interval, RVP_{set} is outside the confidence interval at each RVP_{set} tested except 40% RVP_{set}. Thus, the differences between RVP_{valve} and RVP_{set} are statistically significant at the 5% level (except at 40% RVP_{set}).

With rising RVP_{set} value, RVP_{valve} falls compared to RVP_{set}. At 20% RVP_{set}, RVP_{valve} is 20.4% ± 0.06% whereas at 95% RVP_{set}, RVP_{valve} is 93.6% ± 0.01%. In order to investigate this phenomenon, the ratio of the actual flow rate of the wet line, respectively the dry line, to the set value (multiplied by 100%), was plotted against RVP_{set} (Fig. 2). The set value for the wet or dry flow at a certain RVP_{set} was calculated by multiplying the sum of the flow rates coming out of the wet and the dry line at RVP_{set} with either RVP_{set}/100% to obtain the set value for the wet flow or with (1 − RVP_{set}/100%) to have the nominal value for the dry flow. Fig. 2 shows that for the dry line, the ratio of the measured flow rate to the set value increases considerably at high RVP_{set} values having a value of 128.4 ± 0.02% at 95% RVP_{set}. The ratio for the wet flow, however, is above 100% at 20% RVP_{set} decreasing to a value slightly below 100% at higher RVP_{set} values (differences are significant at the 5% level). Consequently, RVP_{valve} falls compared to RVP_{set} with increasing RVP_{set} value (Table 1).

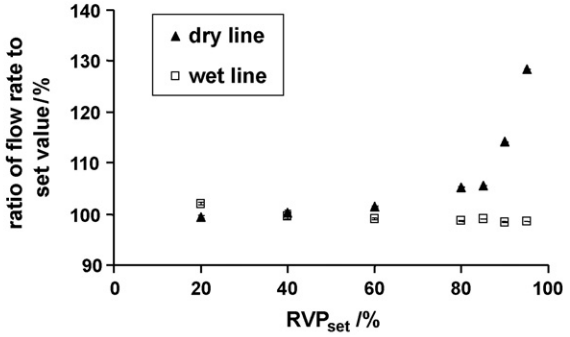

Fig. 2. Ratio of the actual flow rate of the wet line, respectively the dry line, to the set value (multiplied by 100%), plotted against RVP_{set}. The error bars given for each ratio were calculated according to the Gaussian error propagation. They are partly hidden behind the symbols used.

3.2. Verification of the saturation of the wet line

Methanol was chosen as model solvent as it is compatible with the materials of the perfusion unit. Inside the RH perfusion ampoule, methanol was exposed to increasing values of RVP_{set}. Fig. 3 shows the heat flow curve of the first of three identically performed experiments. An endothermic heat flow is observed that decreases from −1144 μW at 80% RVP_{set} to −551 μW at 95% RVP_{set}. The endothermic heat flow is caused by evaporation of methanol. As gaseous methanol was continuously removed by the flowing gas, saturation of the gas phase was not achieved. A constant evaporation rate is reached at each RVP_{set} resulting in steady state heat flows (Fig. 3). The steady state heat flow values are inversely proportional to RVP_{set}, as the evaporation rate increases the lower the activity of methanol in the gaseous phase.

The steady state heat flow values were corrected by subtracting the baseline heat flow of the empty reaction vessel and then plotted not against RVP_{set}, but against the corresponding RVP_{valve} values gained from the volume flow measurements (Fig. 4). The plot shows that the endothermic heat flow measured is linearly related to RVP_{valve}. The data are fitted to a line. Extrapolation of the line yields the heat flow at 100% RVP_{valve} at which only the wet line is open. In case the gas stream entering the reaction vessel via the wet line was saturated with methanol vapours, the heat flow at 100% RVP_{valve} would be zero (intersection with the x-axis) as no evaporation of methanol would occur. Extrapolation of the fitted line however gives an endothermic heat flow of −260 μW at 100% RVP_{valve} revealing that the RVP of methanol of the gas leaving the

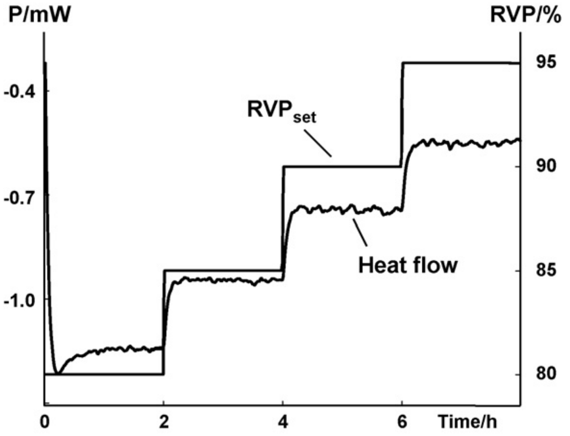

Fig. 3. Heat flow curve obtained from the first of the three identically performed experiments. Methanol was exposed to RVP_{set} values of methanol of 80–95% (T = 25 °C).

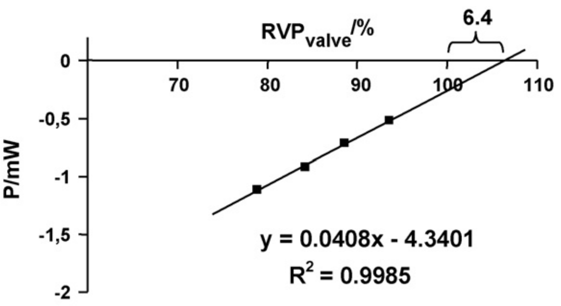

Fig. 4. Steady state heat flow values gained from the first calorimetric experiment plotted against RVP$_{valve}$. The data are fitted to a line that intersects the *x*-axis above 100% RVP$_{valve}$. The offset of the intersection from 100% is given (6.4%).

wet line is below 100% (Fig. 4). The line intersects the *x*-axis at a value above 100%, in this case at 106.4%. The offset of the intersection (106.4 – 100% = 6.4%) corresponds to the amount by which the RVP of methanol of the wet line deviates from 100%. Consequently, the result of the first measurement is that the RVP of methanol of the gas leaving the wet line is 93.6%. The mean value out of three experiments is 93.1% ± 0.26% (standard error).

3.3. *Combination of results to obtain the RVP inside the vessel (RVP$_{in}$) as a function of RVP$_{set}$*

In case of an accurately performing vapour pressure control device, the RVP of solvent inside the reaction vessel, RVP$_{in}$, is slightly higher than the RVP$_{set}$ value defined in the software (except for 0 and 100% RVP$_{set}$). The RVP$_{set}$ value sets the ratio of the volume flows being delivered to the dry and wet line. However, as the volume flow of the gas entering the wet line increases due to the uptake of solvent molecules, a slightly different ratio of the volume flows of the dry and wet line is created inside the reaction vessel. Consequently, RVP$_{in}$ being determined by the ratio of the volume flows inside the vessel differs from RVP$_{set}$. For an accurately working perfusion system, the RVP$_{in}$ at a given RVP$_{set}$ is calculated using the following equation [24]:

$$\mathrm{RVP_{in}} = \frac{1}{1-(P_{\mathrm{Solv,sat}}/P_{\mathrm{tot}})(1-(\mathrm{RVP_{set}}/100\%))}\mathrm{RVP_{set}} \qquad (2)$$

where P$_{Solv,sat}$ is the saturation vapour pressure of solvent at experimental temperature and P$_{tot}$ is the total pressure in the system (equal to the atmospheric pressure). In order to obtain the actual RVP$_{in}$ generated by the tested vapour pressure control device, Eq. (2) is modified using the results of the volume flow measurements and the calorimetric experiments. The resulting equation is:

$$\mathrm{RVP_{in}} = \frac{0.931}{1-(P_{\mathrm{MeOH,sat}}0.931/P_{\mathrm{tot}})(1-(\mathrm{RVP_{valve}}/100\%))}\mathrm{RVP_{valve}} \qquad (3)$$

In Eq. (3), RVP$_{set}$ is replaced by RVP$_{valve}$ since RVP$_{valve}$ describes the actual RVP set by the flow switch valve at a predefined value. Additionally, the factor 0.931 is used to account for the actual RVP of methanol of the wet line.

Using Eq. (3) the RVP$_{in}$ of methanol generated by the tested device at 25 °C and 1.01325 bar was calculated for different values of RVP$_{set}$. The obtained RVP$_{in}$ values are compared with the corresponding values of an accurately working perfusion system (theoretical RVP$_{in}$) (Table 2). Table 2 shows that the actual RVP$_{in}$ is below the theoretical RVP$_{in}$ within the whole RVP range. The absolute deviation from the theoretical RVP$_{in}$ increases with rising RVP$_{set}$. The highest absolute deviation is 7.8% at 95% RVP$_{set}$ whereas the highest relative deviation is found at 60% RVP$_{set}$ being 9.2%.

Table 2
RVP$_{in}$ of methanol at 25 °C and 1.01325 bar using Eq. (2) (theoretical RVP$_{in}$) and Eq. (3) (actual RVP$_{in}$), respectively.

RVP$_{set}$ (%)	Theoretical RVP$_{in}$ (%)	Actual RVP$_{in}$^{a} (%)
20	23.1	21.7 ± 0.23
40	44.4	40.9 ± 0.24
60	64.3	59.0 ± 0.18
80	82.8	75.9 ± 0.09
85	87.2	80.4 ± 0.06
90	91.5	84.0 ± 0.08
95	95.8	88.0 ± 0.03
100	100.0	93.1 ± 0.26

[a] The errors given for the actual values of RVP$_{in}$ at 20% to 95% RVP$_{set}$ were assessed using the Gaussian error propagation.

4. Discussion

The accuracy of the flow switch valve was verified at various RVP$_{set}$ values to cover the whole range of RVP$_{set}$. Special focus was laid on the performance of the valve at high RVP$_{set}$ values as over the years it may happen that the valve having to actively open the wet line fails to fully open the wet line resulting in a back pressure of nitrogen (personal communication with TA Instruments, New Castle, USA). When the valve closes the wet line to open the dry line, the accumulated nitrogen passes through the dry line increasing the volume flow of the dry line above set value. At the same time, the actual wet line flow is below set value. The valve tested seems to show this effect since at higher RVP$_{set}$ values, the ratio of the measured dry line flow to the set value was above 100% whereas the ratio for the wet line flow was below 100% leading to an RVP$_{valve}$ value below RVP$_{set}$ (Fig. 2). The exponential increase of the ratio for the dry line is explained by the fact that the set value for the dry line flow decreases with rising RVP$_{set}$. With decreasing set value for the dry line flow, the impact of the additional nitrogen passing through rises.

In case of an incomplete but precise opening of the wet line, the ratio of the wet flow to the nominal value of f_{wet} should have a value below 100% at all RVP$_{set}$. However, Fig. 2 displays that the ratio exceeds 100% at 20% RVP$_{set}$ decreasing to a value below 100% at higher RVP$_{set}$ values. A possible explanation might be that the valve opens the wet line longer than required. The extension of the opening time of the wet line by a certain time period (constant at different RVP$_{set}$ values) superimposes the incomplete opening of the wet line. At 20% RVP$_{set}$, the elongation of the opening time outweighs the incomplete opening of the wet line leading to a wet flow above set value and a dry flow below set value (Fig. 2). With increasing RVP$_{set}$, the effect of the prolongation of the opening time diminishes whereas the impact of the incomplete opening of the wet line rises.

Concluding one can say that the volume flow measurements provide information about the performance of the flow switch valve. RVP$_{valve}$ calculated from the measured flow rates deviates from RVP$_{set}$ at each RVP$_{set}$ value tested except 40% RVP$_{set}$ indicating a changed performance of the valve. However, as the absolute deviations found are low (maximum difference between RVP$_{valve}$ and RVP$_{set}$ is 1.4% present at 90 and 95% RVP$_{set}$), the question regarding the acceptable accuracy of the valve arises. Since the main focus is to know RVP$_{in}$ and as RVP$_{valve}$ is only one factor in the creation of RVP$_{in}$, the acceptable accuracy of the valve depends on the acceptable accuracy of RVP$_{in}$ which will be discussed below.

It has to be noted that the solvent reservoirs have to be empty during the volume flow measurements. Otherwise, the volume flow coming out of the wet line would not correspond to the volume flow set by the valve but would be increased due to the uptake of solvent molecules. In theory, the saturation of the wet line could have been checked measuring the wet line flow at 100% RVP$_{set}$ having methanol inserted into the solvent reservoirs. However, this method will result in false values for the RVP of methanol of the wet line as gaseous methanol dissolves into the soap film which leads to a decrease in the volume flow. Consequently, the saturation of the wet line was not verified with volume flow measurements, but with the calorimetric experiment.

The testing of the two factors important in the creation of RVP_{in} reveals a lack of saturation for the wet line and a deviation of RVP_{valve} from RVP_{set} (except 40% RVP_{set}). As a consequence, the actual RVP of methanol inside the reaction vessel deviates from the theoretical RVP_{in}. Using Eq. (3), the actual RVP_{in} values at the different RVP_{set} values can be determined. Knowing the actual RVP_{in} values enables the user to adjust RVP_{set} in order to create the desired RVP inside the reaction vessel. Consequently, even though the actual RVP_{in} differs from the theoretical RVP_{in}, the user will be able to reliably perform perfusion calorimetry if the actual RVP_{in} is known. However, in case the actual RVP_{in} differs in such a way from the theoretical RVP_{in} so that the RVP_{in} value required cannot be achieved by adjusting RVP_{set}, the accuracy of the vapour pressure control device is not acceptable. Hence, the acceptable accuracy of the device depends on the RVP_{in} value which is desired, i.e. on the design of the experiment. The accuracy of the tested device, for example, is acceptable for all experiments requiring a maximum RVP_{in} of methanol equal to or less than 93.1%. If an improved accuracy of the tested device was requested, the main focus would be to enhance the accuracy of the RVP of the wet line. As the RVP of the wet line is assumed to depend on the time period the nitrogen bubbles through the solvent, possible measures in order to try to increase the RVP would be a lowering of the flow rate and a check whether the penetration of the steel tubes into the solvent is maximal. It has to be taken into account that the RVP of the wet line may change in case another solvent is used or in case the experiment is performed at another temperature. Therefore, the RVP of the wet line has to be reassessed when changing the solvent or the operating temperature.

Additionally, as the valve was found to have a changed performance, it is recommended to repeat the volume flow measurements at regular intervals, as the performance of the valve might deteriorate.

5. Conclusions

The method developed is suitable to check the present vapour pressure control device. The testing of the flow switch valve and the verification of the saturation of the wet line allows the determination of the actual RVP of methanol inside the reaction vessel. As the method described is not limited to specific solvents, the RVP_{in} of any solvent can be assessed provided that the solvent chosen is compatible with the materials of the perfusion unit. In addition, the method is not restricted to systems based on a flow switch valve. It may also be applied for devices operating with two mass flow controllers. The knowledge of the RVP_{in} enables the user to reliably perform perfusion calorimetry, e.g. to ascertain the RVP at which an amorphous powder crystallises or a polymorphic substance transforms into a solvate.

Acknowledgements

The authors would like to thank Dr. Peter Vikegard from TA Instruments for helpful discussions and valuable comments. This work was funded by Bayer Animal Health GmbH.

References

[1] C. Ahlneck, G. Zografi, Int. J. Pharm. 62 (1990) 87–95.
[2] G. Buckton, J.W. Dove, P. Davies, Int. J. Pharm. 193 (1999) 13–19.
[3] K. Fiebich, M. Mutz, J. Therm. Anal. Calorim. 57 (1999) 75–85.
[4] M. Angberg, C. Nystrom, S. Castensson, Int. J. Pharm. 81 (1992) 153–167.
[5] M.N. Vemuri, Z. Chrzan, R. Cavatur, J. Therm. Anal. Calorim. 78 (2004) 47–54.
[6] A. Columbano, G. Buckton, P. Wikeley, Int. J. Pharm. 237 (2002) 171–178.
[7] M. Angberg, C. Nystrom, S. Castensson, Int. J. Pharm. 83 (1982) 11–23.
[8] E. Yonemochi, Y. Inoue, G. Buckton, A. Moffat, T. Oguchi, K. Yamamoto, Pharm. Res. 16 (1999) 835–840.
[9] R.M. Samra, G. Buckton, Int. J. Pharm. 284 (2004) 53–60.
[10] K. Kawakami, T. Numa, Y. Ida, J. Pharm. Sci. 91 (2001) 417–423.
[11] H. Ahmed, G. Buckton, D.A. Rawlins, Int. J. Pharm. 130 (1996) 195–201.
[12] G. Buckton, P. Darcy, D. Greenleaf, P. Holbrook, Int. J. Pharm. 116 (1995) 113–118.
[13] S. Gaisford, G. Buckton, Thermochim. Acta 380 (2001) 185–198.
[14] V.-P. Lehto, E. Laine, Int. J. Pharm. 163 (1998) 49–62.
[15] L. David, B. Aziz, P.M. Danforth, Pharm. Res. 20 (2003) 308–318.
[16] D.F. Jakobsen, S. Frokjaer, C. Larsen, H. Niemann, A. Buur, Int. J. Pharm. 156 (1997) 67–77.
[17] I.L. Timmermann, H. Steckel, M. Trunk, Eur. J. Pharm. Biopharm. 64 (2006) 107–114.
[18] Thermometric AB, Sweden, Experimental & Technical Note EN 013 c (2001).
[19] N.M. Vemuri, C. Zofia, C. Raghu, J. Therm. Anal. Calorim. 78 (2004) 55–62.
[20] L. Mackin, R. Zanon, J.M. Park, K. Foster, H. Opalenik, M. Demonte, Int. J. Pharm. 231 (2002) 227–236.
[21] G. Buckton, Thermochim. Acta 347 (2000) 63–71.
[22] P.M. Danforth, L. David, Pharm. Res. 23 (2006) 2291–2305.
[23] P.L. Sheridan, B. Graham, D.E. Storey, Pharm. Res. 12 (1995) 1025–1030.
[24] Thermometric AB, Sweden, Experimental & Technical Note EN 013 a (2000).