



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

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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.

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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 vari-

ous 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

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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

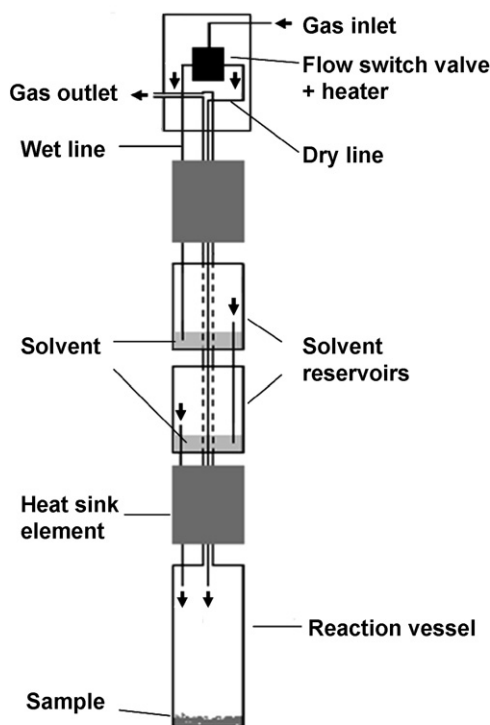


Fig. 1. Schematic drawing of the RH perfusion ampoule and the flow switch valve.

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 $3000 \mu\text{W}$. 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.

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.

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