



Design, Testing and Pharmaceutical Applications of a Gas Pressure Controller Device for Solid - Gas Microcalorimetric Titration

A. Bakri

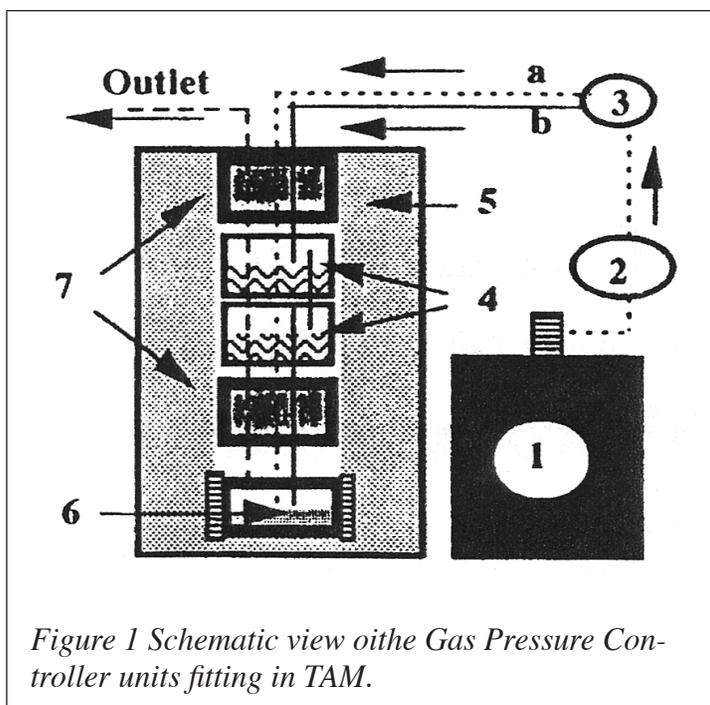
University Joseph Fourier Faculty of Pharmacy Pharmaceutical
Engineering Avenue de Verdun 38240 Meylan, France

INTRODUCTION

Interactions between water and component materials take place in all steps of dosage from manufacture. These interactions can affect the mechanical, physical and chemical properties and consequently also the behaviour of the material of interest.

The use of the Thermal Activity Monitor (TAM) is already well established in the field of compatibility and stability testing of pharmaceutical preparations and other chemicals in general. The sample is loaded into a sealed ampoule which is placed in the measuring position of the TAM. The recorded heat flux (P) can be related to the reaction rate and the reaction enthalpy (refs. 1-4). However, such a closed system does not allow any control or change of experimental factors such as oxygen pressure or water vapour pressure in the ampoule during an ongoing experiment. In order to overcome this limitation, the Gas Pressure Controller device has been specifically developed to control, in particular the relative humidity (RH) within the sample ampoule (fig. 1). During a calorimetric experiment, dry gas (1) is delivered by a flow rate controller (2) to a switching valve (3). In one position, a, the valve delivers dry gas directly to the sample ampoule. In the other position, b, the gas is passed through two humidifier reservoirs (4) in thermal contact with the calorimetric bath (5), and the gas it is then saturated with water (100 % RH) before reaching the sample (6). Both dry (0 % RH) and wet (100 % RH) gas pass separately through heat exchangers (7) for thermal equilibration. The incoming RH to the sample can be controlled from the valve and varied from 0 to 100 % by mixing various ratios of dry and wet gas.

The device operates with a precision better than ± 0.1 % RH within the range of 0% and 100% RH throughout the operating temperature of the TAM. It is possible to program the RH through the Digitam software



either as a series of discrete steps or as an upward or downward ramp.

The very rapid response to changes in RH makes this instrument system a powerful tool for determining sorption isotherms and surface energies within a few hours. Only small amounts of material are needed. Typical sample loadings for powders are on the order of 50 to 200 mg.

EXPERIMENTAL

A liquid or solid sample is placed in the measuring ampoule as shown in figure 2. The exchange between the incoming RH-controlled gas may take place at the upper geometrical sample surface (overt) or at the total exchange surface when a powder is analyzed. If the latter option is preferred, the outlet is lowered down and the gas is passed through the powder bed (right).

Liquids: The effect of RH upon water evaporation thermograms has been studied at various flow rates using air or N₂ as carrier. A typical thermogram is shown in figure 3.

This relationship was used to calorimetrically determine the RH-values of standard salt solutions of known RH. The standard solutions were placed in a thermostated bath at 25°C outside the calorimeter. Air was then pumped through the standard solution directly to the measuring ampoule (via the dry inlet) containing water. The thermograms and their interpretation are shown in figures 5 and 6.

The physical modelling and the mathematics behind these results will be published soon.

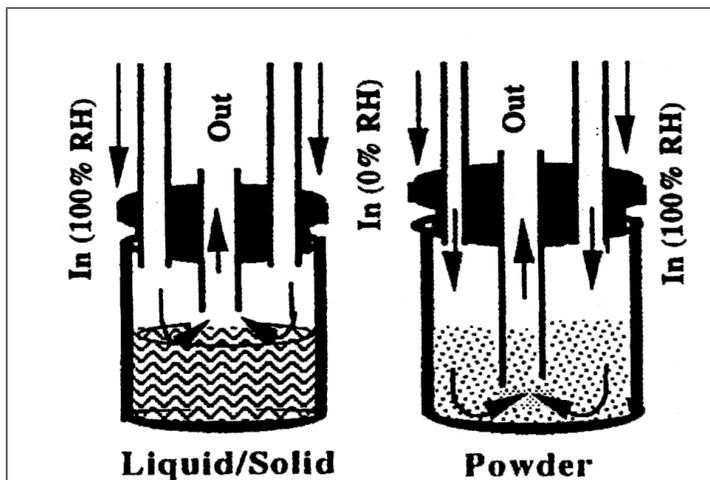


Figure 2. Sample disposition in the ampoule

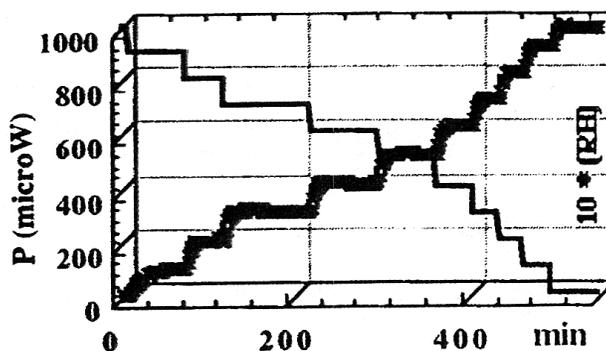


Figure 3. Effect of RH on water evaporation thermograms ($f=100$ ml/h, $T=25^\circ\text{C}$)

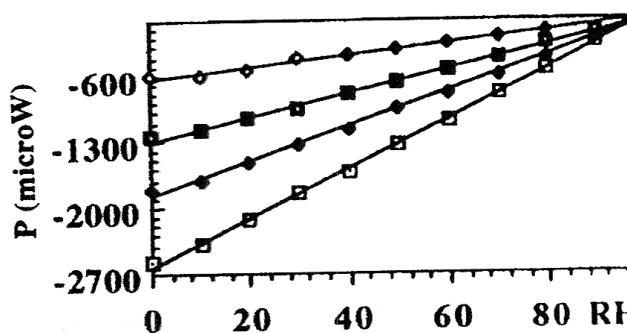


Figure 4 shows the effect of the gas flow rate on water evaporation heat flux at 25°C: \diamond (50 ml/h) \square (110 ml/h) \blacklozenge (160 ml/h) \square (220 ml/h)

Powders: As an example of a solid material, the results of calorimetric sorption isotherms of a pharmaceutical polymeric material are presented here. 150 mg of the material was placed in the measuring ampoule and dried under 0 % RH ($f=100$ ml/h) until zero heat flux was observed. The incoming RH was then set to 10 % and a positive adsorption response was recorded. When the equilibrium was reached (P equals zero) the incoming RH was set to zero and a desorption isotherm ($P < 0$) was then observed. At equilibrium, another up and down scan was carried out successively with 20 % RH, 30 % RH, 40 % RH, etc. The absorption/desorption results are shown in figure 7.

Similar experiments were carried out at other temperatures (40 °C and 50 °C). Figure 8 shows a plot of the total adsorption heat as a function of the imposed vapour pressure.

It can easily be shown that a plot of \ln (vapour pressure) at constant Q_{ads} against $(1/T)$ is equivalent to a van't Hoff plot (to be published) and gives a straight line from which the adsorption enthalpy can be derived (figure 9). Knowing the vapour adsorption enthalpy, it is easy to calculate the amount of water adsorbed to the polymer at a given RH and temperature (in this case 12 % adsorbed water at 65 % RH and 25 °C). Adsorption isotherms expressed in mass of water adsorbed per total mass can then be obtained.

Other thermodynamic parameters such as the adsorption entropy and equilibrium constant values can be derived.

This method can also be used as a "solid surface energies titration mapping" when one studies the enthalpy variation with RH and temperature.

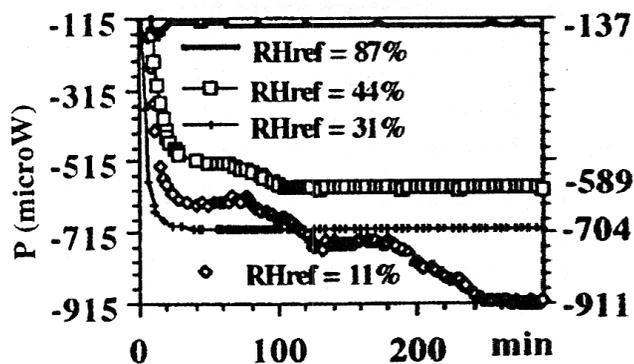


Figure 5. Water evaporation thennograms; Incoming air from standard salt solutions ($f=100$ ml/h. $T=25$ °C)

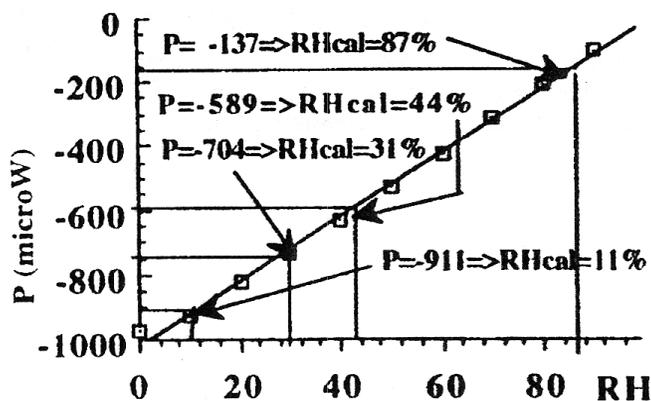


Figure 6. RH 01 standard salt solutions determined from water evaporation calorimetric data

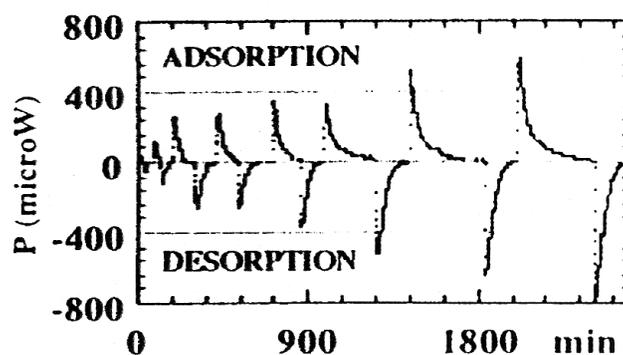


Figure 7. Polymer...at vapour sorption thermogram. $T=25$ °C. RH scan up and down from 0 to 80 %.

CONCLUSION

The very rapid response to RH changes makes this instrument system a powerful tool for determining sorption isotherms and surface energies within the space of only a few hours. Using the ramp method (see introduction) for the determination of the effect of humidity on physical changes of pharmaceutical preparations is nowadays of routine work in our laboratory. Examples of physical changes ex stability are polymorphism and change from amorphous to crystalline state. Moreover, the method makes it possible to determine optimal RH storage or handling conditions of e.g. effervescent pharmaceutical preparations. The method is nondestructive and it is shown to be of the level of sensitivity that allows measurements to be carried out at ambient temperature. Only small amounts of material are needed.

Potential applications of this instrument system include the evaluation of vapour diffusion through plastics or coating material, specific surface area and surface energy determinations. The author is currently working in these areas and proposes to publish further data in the near future.

ACKNOWLEDGEMENTS

The author wishes to thank Dr. Kennici from L'OREAL for providing the microcalorimeter.

This Application Note is dedicated to Dr. L. G. Svensson, Celsius Materials Technology, for being pioneer in this field.

REFERENCES

1. Russel, S., Calculations for the prediction of long-term stability using the thermal and kinetic parameters measured by the Thermal Activity Monitor. *ThermoMetric Application Note 22019*, ThermoMetric AB. December 1992
2. Bakrl, A., Janssen, L.H.M. and Wilting, J., Flow microcalorimetry applied to the study of chemical stability of organic compounds. *J. Therm. Anal.* 33, 1193-1199. 1988
3. Bakrl, A., Xirong N. and Janssen, L.H.M., Effect on its stability of inclusion of ben-

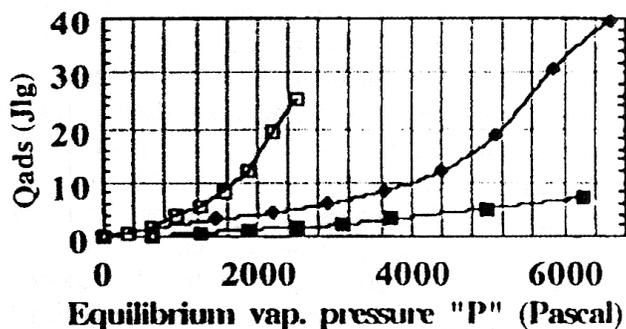


Figure 8. Effect of vapour pressure on the polymer's adsorption heat at various temperatures. a $T=25$ °C, b $T=40$ °C, c $DT=50$ °C

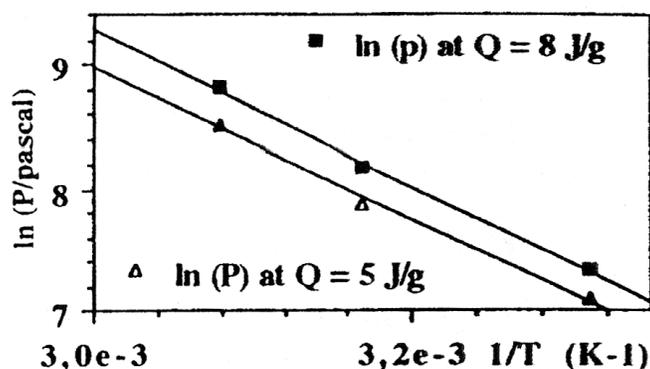


Figure 9. Van't Hoff plot of the polymer-vapour adsorption obtained from calorimetric data at 25 °C, 40 °C and 50 °C.

zocaine in betacyc10dextrin as studied by conduction microcalorimetry. In: *Minutes of the Fifth International Symposium on Cyclodextrins*, Editions de Santé Publishers, Paris, pp. 261-266, **1990**

4. Svensson, L.G., Microcalorimetric measurement of the rate of diffusion of water through a plastic barrier: *ThermoMetric Application Note 22001*, ThermoMetric AB. December 1990