Microcalorimetric Characterization of Physical Changes in Solid State Drugs

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INTRODUCTION

Particle size reduction (grinding, micronization) is a common process when dealing with powder technology, as is the case in the pharmaceutical, chemical and food industries.

When crystalline compounds are exposed to such mechanical stress, disturbances occur in their structure due to the creation of amorphous regions. These regions exhibit physical and/or chemical properties quite different to those areas remaining crystalline. Such a change in the degre1e of crystallinity may affect the mechanical (e.g. flow properties), the physical (e.g. solubility), chemical (Ie.g. stability) and pharmacological (e.g. bioavailability) properties of the powder. Moreover, further pharmaceutical processing of the powder depends strongly on its degree of amorphicity. Even if the sample is amorphous only Ito a small extent, this can be of critical importance since these regions will mainly be present on the surfaces of the particles.

An amorphous compound can be recrystallized by simply raising the temperature above its temperature of crystallization (T d. However. in practice this temperature can be changed significantly by the presence of vapourised water molecules absorbed by the powder. It is thus of vital importance to investigate the effect of relative humidity (RH) on the compound of interest.

This application note reports on the use of amicrocalorimeter equipped with a controlled RH perfusion ampoule to characrerize a micronized drug with respect to RH. The device used in ti1eseexperiments was based on the original design of Dr A. Bakri, University Joseph Fourier, France[1].

EXPERIMENTAL

The experiments were performed in the ThermoMetric 2277 Thermal Activity Monitor (TAM), equipped with the standard ampoule calorimetric units. The sample was placed in a vapour perfusion ampoule and perfused with known proportions of completely dry (0% RH) and completely saturated (100% RH) nitrogen gas. By keeping the total flow rate constant and varying the ratio of dry to saturated gas, any relative humidity could be obtained in the ampoule.

The ampoule was charged with 30-50 mg of the drug. Before starting the experiment, the sample was left to equilibrate at 0% RH and, in most cases, at a temperature of 25°C. The relative humidity was changed either in a continuous ramp or in steps of 10%.

Pure substances as wen as mixtures of two solids were investigated in this study. AU sample handling took place in a room where the RH was controlled to 20%.

RESULTS

Figure 1 shows a typical heat flow curve for a micronized pure substance when exposed to a continuous change in RH at constant rate.

Several phases can be distinguished all of which agree well with the known behaviour of a crystalline substance with amorphous regions. The curve can be clearly divided into three phases, absorption, crystallization and evaporation of excess water following crystallization. Since the change in RH can be made very slowly and it is an open system, the sample is in a state of "near equilibrium". Hence, it is possible to obtain information about the specific RH at which recrystallization actually takes place.

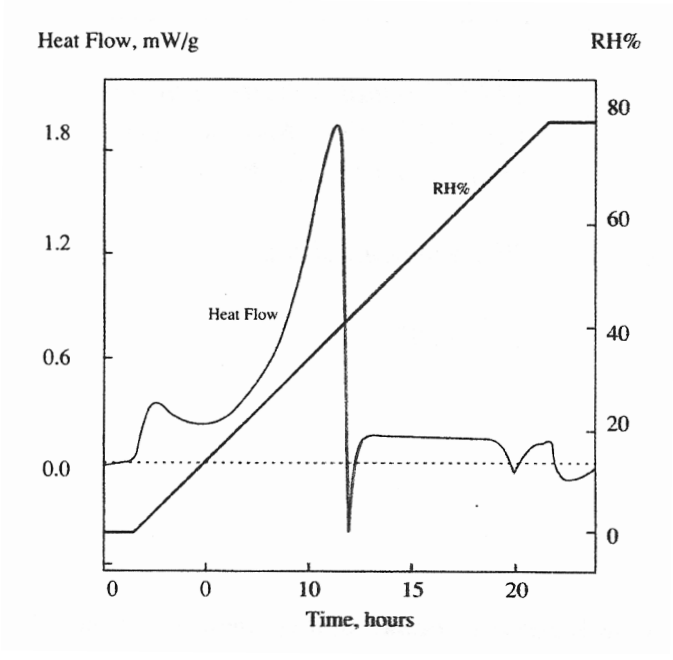

Fig. 1 Heat flow from a micronized pure sample exposed to a continuous constant increase in RlI

Apart from this more qualitative approach it is also possible to integrate between any two RH values and obtain precise values of the heat evolved or absorbed during the process.

Figure 2 shows the heat flow from a micronized mixed sample under conditions of a stepwise increase in RH.

In this figure it can be seen that the two compounds will recrystallize at quite different RH values. In this case, peaks are obtained (due to absorption) for each increase in RH. The recrystallizations are seen as an increased peak height and an endothermic evaporation of excess water.

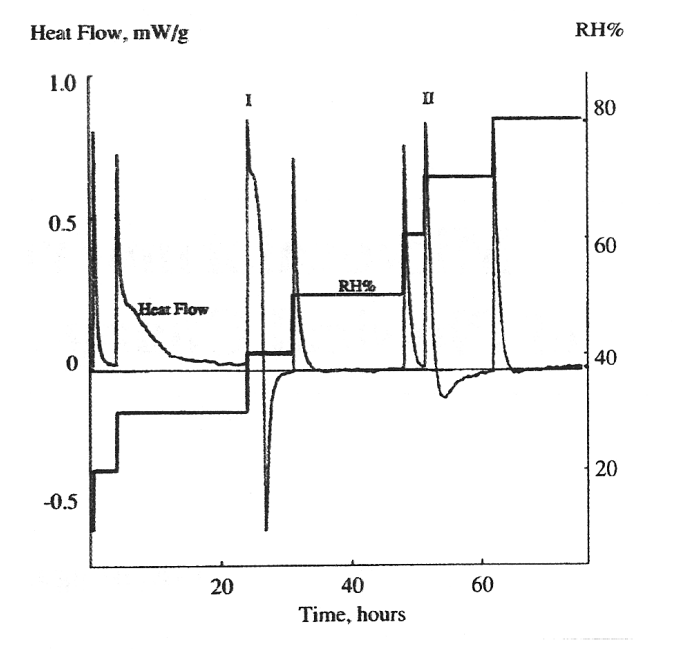

Fig. 2 Heat flow from a micronized mixed sample exposed to a stepwise increase in RH

CONCLUSION

This microcalorimetric technique has proved to reveal several characteristics of ground solids in a single experiment. The information obtainable is not only if a sample is affected by changes in RH but also *at which* RH it is affected and *how much* energy is involved in the process. Furthermore, this can

be performed on samples with disturbances in the crystalline structure which are too small to detect with conventional techniques like X-ray crystallography.

It should also be of great interest to examine solids containing other types of RH sensitive regions, e.g. amphifiles in the same way, or to use solvents other than water.

This technique confirms that the microcalorimeter is a versatile instrument and a very useful tool in pharmaceutical processing and development.

REFERENCES

1. A. Bakri, "Design, Testing and Pharmaceutical Applications of a Gas Pressure Controller Device for Solid-Gas Microcalorimetric Titration", ThermoMetric Application Note 22021. **1993**