

Improvement of the Experimental Testing Method for the Determination of the Influence of Air on the Thermal Stability of Chemical Compounds

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Abstract:

In the chemical industry, compounds are often dried in fluidized bed dryers or in spray dryers. Several explosions due to the induction of highly exothermal decomposition reactions in the presence of an air flow have occurred in the past. Therefore, the thermal stability of chemical substances is usually investigated in the presence of air. Nevertheless, most of the tests are actually performed with DTA devices equipped with open testing vessels (Lütolf and Grewer ovens, RADEX, etc.). Due to the potential high biological activity of some pharmaceutical substances and the potential toxicity of decomposition compounds, the utilization of these methods represents a risk for the laboratory operators and can lead to environmental problems. A new method based on DSC experiments performed with closed crucibles in the presence of oxygen is proposed and discussed. It leads to significant improvements of the working conditions from a HSE (Health, Safety, Environment) point of view (no exposure to toxic decomposition compounds, no gas release in the environment). Moreover, the small sample amounts required for testing lead to a cost reduction for some very expensive pharmaceutical substances.

Introduction

The goal of drying processes is to remove a solvent from a suspension, slurry, or damp powder to obtain a dry powder.

- In a fluidized bed dryer,¹ heated air is passed via a plenum chamber and a diffuser plate into the fluidized bed of material, from which it passes to a dust separator. Wet material is fed continuously into the bed and mixes immediately with the dry charge. Dry material overflows via a drain to an integral after-cooler.

- In a spray dryer,² the wet mixture is sprayed in the top part of the dryer volume, where it encounters a co- or counter-flowing stream of hot air. Heat transfer and mass transfer are accomplished by direct contact of the hot gas with the dispersed droplets. As the particles fall through the dryer volume, the solvent is driven off, and the dry powder is collected at the bottom by a vibrofluidizer or separated from the air stream by a cyclone.

After drying, the obtained product is usually transferred to a storage or packaging unit.

The fire and explosion hazards associated with the operation of such dryers are well recognized. The possible safety measures are described in the literature (explosion venting, explosion suppression, etc.). In some cases, the drying must be performed under inert conditions to avoid the thermal oxidation of air-sensitive substances. Even if the drying operation itself is performed under an inert atmosphere, discharge of hot powder, storage of warm powder, or inadvertent loss of inertization during drying needs to be considered so that the maximum safe working temperatures can be determined.

Therefore, thermal stability tests are usually performed in the safety laboratories in the absence and in the presence of air to identify air-sensitive compounds. These tests are often done with devices using the differential thermal analysis (DTA) principle equipped with open tubes. Due to the potential high activity of some pharmaceutical substances and the toxicity of decomposition compounds, the utilization of these methods represents a risk for the laboratory operators and also environmental problems.

In some cases, the tests are carried out with sealed Carius tubes. The sample is charged to a fill level of ca. 30%, and the remaining headspace is filled with air. However, even this method cannot reliably reproduce the entry of an air flow in a drying apparatus.

The aim of this report is to describe a new method based on differential scanning calorimetry (DSC) experiments performed with closed crucibles in the presence of oxygen.

Classical Testing Devices. Many safety laboratories are equipped with a Lütolf oven, a Grewer oven, RADEX (rapid detector for exothermic processes^{3,4}), or equivalent devices. These methods are based on the measurement of the temperature difference ΔT between the sample and a reference (or, with equipment having no reference, between sample and oven) as a function of time or oven temperature.

With the Lütolf oven,⁵ the test is performed with an open tube under a poor air atmosphere. The apparatus is made of a heated metal block for six testing tubes with a temperature regulation and recording device for the oven and sample temperatures (see Figure 1).

On the other hand, the measurements are performed with an air flow with the Grewer oven.⁶ The sample and the reference are placed in small cylindrical wire baskets. Warm air goes through these compounds, and the temperature

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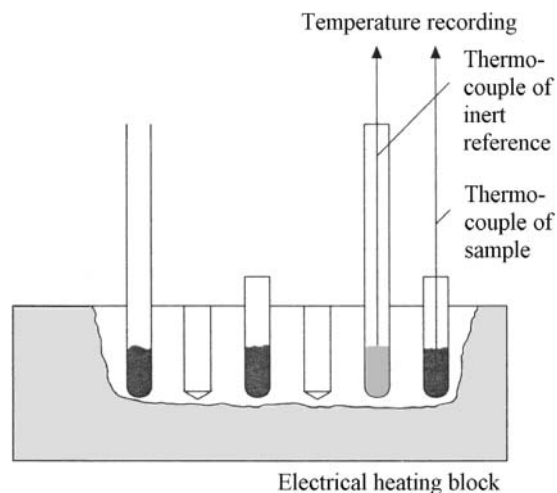


Figure 1. Lütolf apparatus for the determination of the onset temperature of a decomposition reaction.

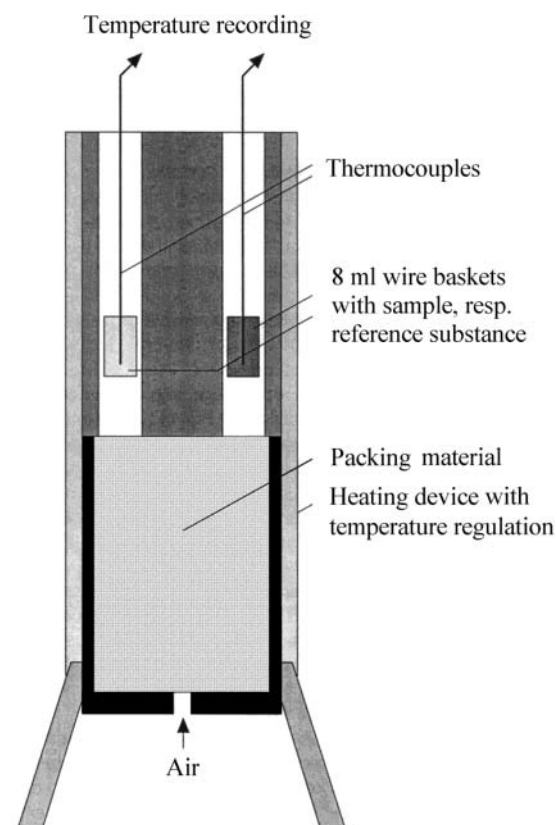


Figure 2. Grever apparatus for the determination of the onset temperature of a decomposition reaction in an air stream.

difference between the sample and the inert reference is registered (see Figure 2).

The comparison of the obtained results allows the detection of an influence of air on the thermal stability of the investigated sample.

Several other methods specially designed to replicate varying air availability in industrial situations are described in the literature:^{7,8}

- In the diffusion cell test, the open cell with a sintered glass base is filled with powder, and air diffuses naturally through the substance.

- In the aerated cell test, the same equipment is used except that a closure is placed on the diffusion cell, and a flow of preheated air is continually purged through the sample for the duration of the test.

- In the air over layer test, a thin layer of material over which preheated air is continually purged is utilized.

These tests also give reliable and accurate results for the assessment of the influence of an air flow on the thermal stability of a compound.

Similar results are obtained by using RADEX devices. In this case, the comparison is easier because the experiments in absence or in the presence of an air flow are performed in parallel identical ovens. Four sample tubes are usually prepared for the following test conditions:

(A) air open: tube open against normal atmosphere;

(B) in air stream: permanent flushing of the sample with air (5 L/h) preheated to the oven temperature;

(C) in argon stream: permanent flushing of the sample with argon (5 L/h) preheated to the oven temperature (nitrogen may be used as an alternative);

(D) air closed: in an autoclave filled with air.

For each DTA test the temperature difference between the sample and a stored temperature curve from an inert reference material (ΔT signal) is plotted against the oven temperature.

According to the guidelines in effect at our company, a decomposition is said to be dependent on air if the onset of the exotherm is at least 30 °C higher under inert conditions (C) than in contact with air (A and B). This criterion can be slightly different from one company to another. The heating rate of the experiments and the detection limit of the ovens should be the same for the experiences in the presence or in the absence of air to be able to compare the temperature of the onset of decomposition reactions.

If in the autoclave (D) an exotherm observed which—in the open tubes—is hidden by evaporation of residual solvent, more detailed investigations may be necessary.

The results obtained with these devices are of a qualitative order. Nevertheless, they are sufficient to get straight the influence of air on the thermal stability of a chemical compound. Figure 4 shows thermograms obtained with RADEX ovens (Foron brown dye). A highly exothermal decomposition reaction is observed above ca. 125 °C in the presence of an air stream. This substance should not be dried at high temperatures in an air flow. However, no safety-relevant decomposition reaction is observed in an argon flow. A leakage of the autoclave occurs above ca. 270 °C (endothermic phenomenon due to the sudden release of material). The experiment performed with the open tube against normal air atmosphere shows only a small exothermal signal above ca. 125 °C. The drying of the investigated substance must be performed under an inert atmosphere using argon or nitrogen.

However, some difficulties can occur when these classical methods are used.

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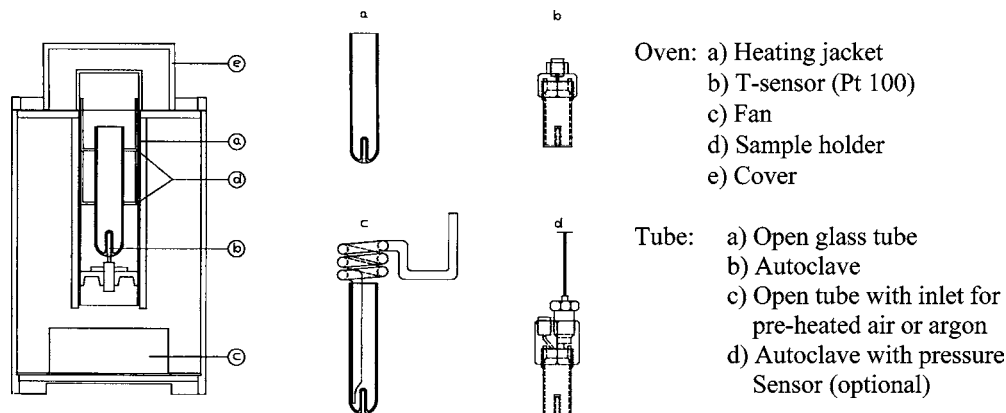


Figure 3. RADEX device for the determination of the onset temperature of a decomposition reaction.

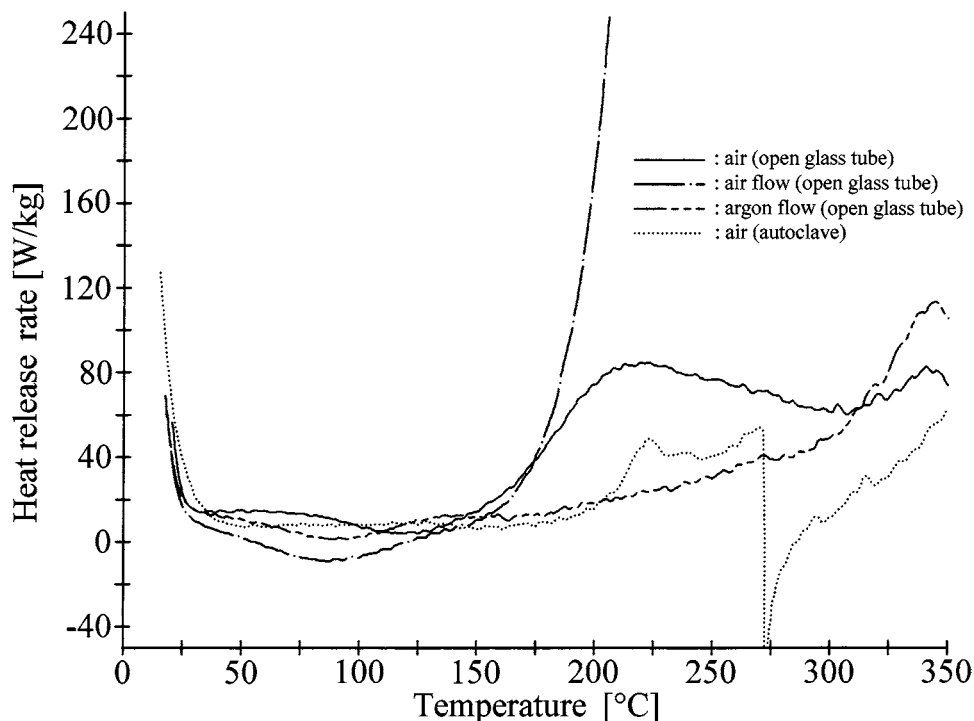


Figure 4. RADEX experimental results (Foron brown dye).

- An exothermal reaction can be partly hidden by the endothermal signal resulting from the evaporation of the remaining solvent.⁹ Therefore, the utilization of closed autoclaves should be preferred to avoid this phenomenon. Such a test is performed with the RADEX device, but not when using Lütolf and Greuer ovens (however, the results are only qualitative).

- About 10 g of substance is required to perform these tests. During the decomposition of the substance, toxic degradation compounds may be formed (e.g., dioxins). A portion of these decomposition substances is carried away in the ventilation of the fume hood, leading to a potential environmental pollution; a remaining part stays in the testing tubes leading to a possible contamination of the laboratory operator during the cleaning of the equipment after completion of the experiments. A significant reduction of the sample amount is desirable. Here, too, the utilization of closed testing

vessels avoids the contamination with toxic decomposition substances.

Therefore, DSC which is routinely used for screening testing of the thermal stability of chemical substances can potentially offer a good alternative to these experimental methods. It is probably the most common screening technique in use today and has been in use for many years in a number of different areas of chemistry, not only safety investigation.¹⁰

Experimental Section

Fourteen different chemical compounds were chosen for this work (dyes and pharmaceutical substances). The thermal stability of 12 of them was classified as being dependent on the presence of an air flow using the RADEX tests; for the other substances, no influence of the atmosphere was observed with the same method.

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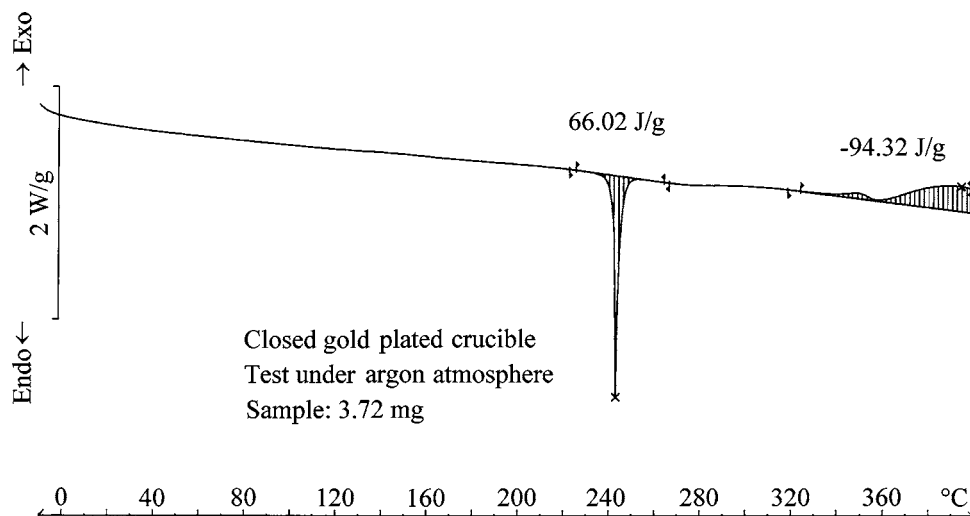


Figure 5. Dynamic DSC thermostability test under argon atmosphere (Polysynthren blue dye).

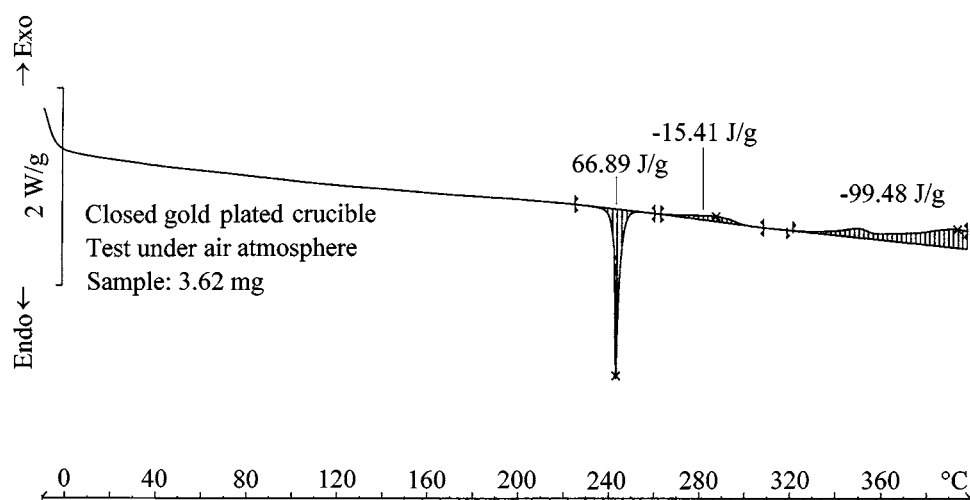


Figure 6. Dynamic DSC thermostability test under air atmosphere (Polysynthren blue dye).

1. Comparison between Tests Performed under Air and Argon Atmospheres. The experiments were performed using the following equipment and procedures:

| | |
|-------------|--|
| apparatus: | Mettler DSC821 |
| atmosphere: | samples were weighed in the presence of air, respectively of argon typical sample weight: ca. 5 mg |
| vessel: | closed gold plated stainless steel crucibles, pressure resistant (ca. 200 bar), sample volume 45 μ L, weight-adjusted to reference crucible (1%) |
| technique: | temperature ramp 4 $^{\circ}$ C/min from -10 $^{\circ}$ C up to 400 $^{\circ}$ C |

The comparison of the tests performed under both atmospheres shows for most of the samples a higher heat of decomposition under air than under argon. Nevertheless, the energy difference between both experiments is not always significant enough (see Figures 5 and 6; Polysynthren blue dye). The energy of the decomposition reaction starting above ca. 320 $^{\circ}$ C is comparable in the presence of air or argon (ca. -95 kJ/kg between 320 and 400 $^{\circ}$ C). Under air pressure, an additional weakly exothermic reaction was observed at ca. 260 $^{\circ}$ C (about -15 kJ/kg). The accurate evaluation of this exothermic reaction depends strongly on the shape of the

baseline and is not unequivocal. Therefore, this method cannot be used to reliably predict the influence of a sudden entry of an air flow in a drying system. Moreover, the investigated compound is very sensitive to an air flow as shown during the RADEX experiments (see Figure 7).

However, the results obtained using RADEX ovens for samples which show no influence of air on the thermal stability are confirmed using these DSC experiments under argon or air atmosphere.

The next step of this work was to develop a method with a larger air amount in comparison with the investigated sample amount.

2. Comparison between Tests Performed under Air and Argon Pressure. The experiments were performed using the following equipment and procedures:

| | |
|-------------|--|
| apparatus: | Mettler DSC27HP |
| atmosphere: | experiments under air, respectively argon pressure (30 bar) typical sample weight: ca. 5 mg |
| vessel: | open aluminum crucibles, sample volume 40 μ L, weight-adjusted to reference crucible (1%) |
| technique: | temperature ramp 1 $^{\circ}$ C/min from 30 $^{\circ}$ C up to 400 $^{\circ}$ C |

In contrast to the previous experiments, the tests were

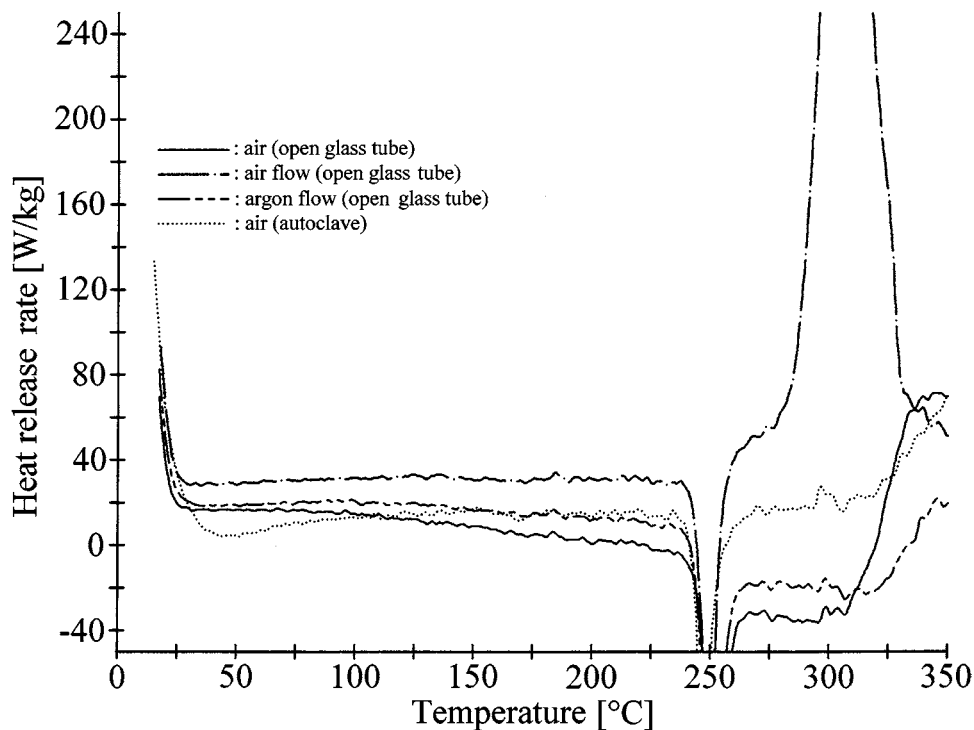


Figure 7. RADEX thermostability tests (Polysynthren blue dye).

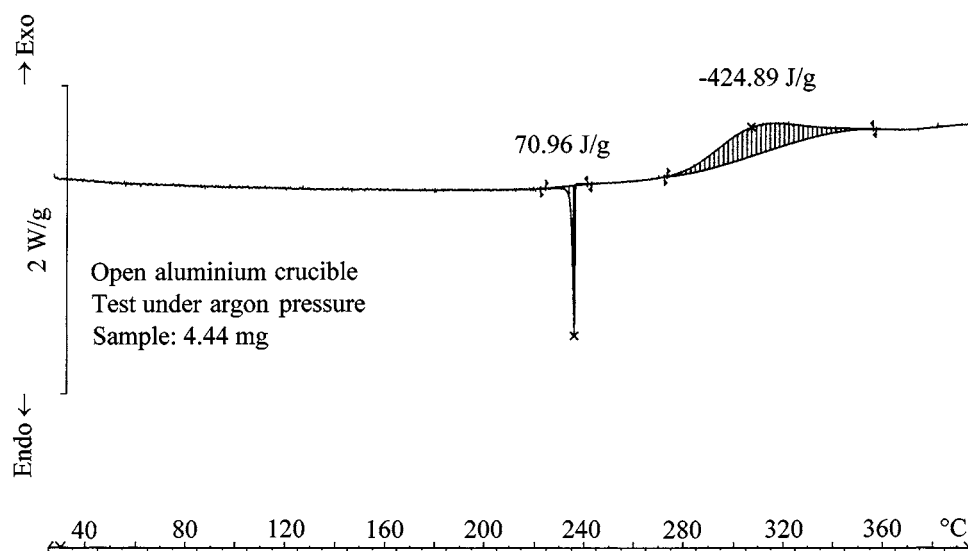


Figure 8. Dynamic DSC thermostability test under argon pressure (Polysynthren blue dye).

performed with open crucibles under a constant gas pressure. The DSC device used can be operated between 1 and 70 bar and up to 600 °C. It is equipped with a bursting disk to avoid an overpressure in the measuring cell. The measurements are started after the pressurization of the cell.

For the samples sensitive to an air flow according to the RADEX tests, the DSC measurements performed under air pressure show very large exothermic reactions compared with the one done under argon atmosphere (see Figures 8 and 9; Polysynthren blue dye). The measured energy is higher than -9273 kJ/kg under air pressure and about -425 kJ/kg under argon pressure. In this later case, the shift obtained in the experimental plot is probably mainly due to the dissipation of ca. 22% of the substance out of the crucible (i.e. it probably does not correspond to a real exothermic degrada-

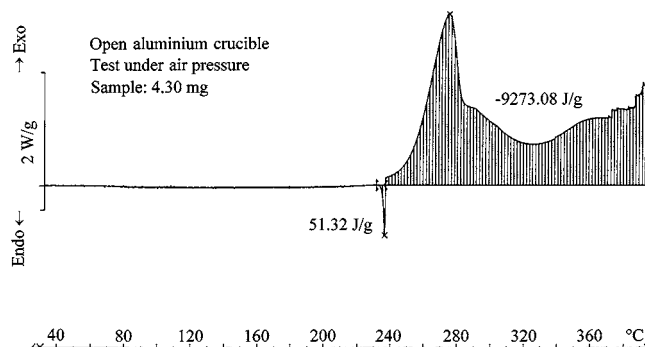


Figure 9. Dynamic DSC thermostability test under air pressure (Polysynthren blue dye).

tion reaction). In the same way, the measured heat of decomposition under air pressure is not accurate, due to the

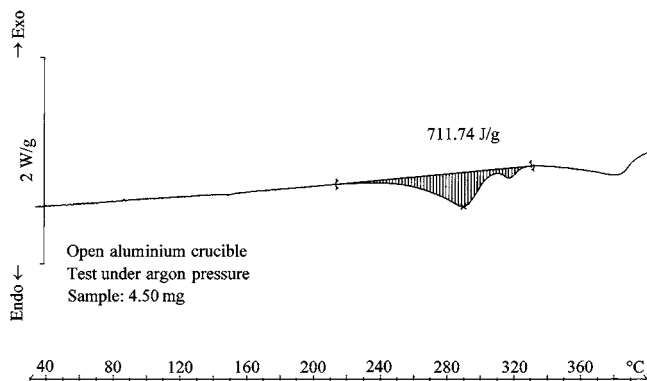


Figure 10. Dynamic DSC thermostability test under argon pressure (Feliderm Bate PB1).

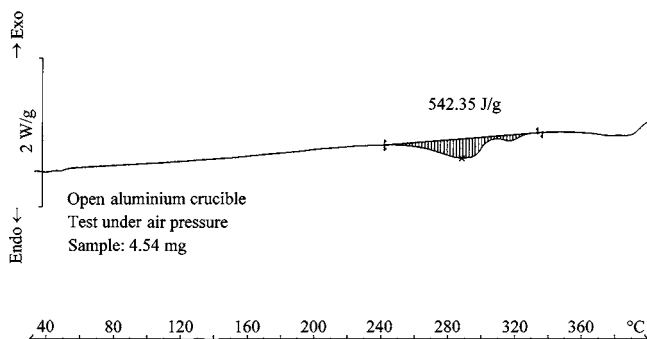


Figure 11. Dynamic DSC thermostability test under air pressure (Feliderm Bate PB1).

dissipation of ca. 84% of the sample amount during the completion of the experiment (probably mainly due to the formation of decomposition gases). However, the signal measured in the presence of air is much larger than in the presence of argon.

For substances which are not sensitive to air flow according to RADEX tests, the experiments performed with the pressure DSC show no significant difference between the test done under argon or air pressure (see Figures 10 and 11; Feliderm Bate PB1).

This method can be used for the determination of the influence of air on the thermal stability of chemical substances. Nevertheless, it is not really adapted to an industrial environment. The duration of the experiment is much longer than with DSC using classical closed crucibles due to the relatively time-consuming preparation of the testing equipment and to the slower heating rate of the apparatus (necessary to keep a good baseline at high pressures). In this way, it seems to be difficult to use this method routinely in a safety laboratory in which hundreds of samples should yearly be tested.

Moreover, the operator is confronted with occupational hygiene problems during the cleaning operation after completion of the experiment. The dissipated degradation substances are distributed in the testing vessel which should be cleaned between each experiment. Furthermore, the presence of decomposition substances in the oven (even in small amounts) can lead over the course of time to a failure of the testing device.

The next step of this work was to develop a method which can be used routinely in an industrial safety laboratory.

3. Comparison between Tests Performed under Argon and Oxygen Atmospheres. The experiments were performed using the following equipment and procedures:

| | |
|-------------|---|
| apparatus: | Mettler DSC821 |
| atmosphere: | samples were weighed in the presence of argon or oxygen, respectively typical sample weight: ca. 5 mg (argon); ca. 1 mg (oxygen) |
| vessel: | closed gold plated stainless steel crucibles, pressure resistant (ca. 200 bar), sample volume 45 μ L, weight-adjusted to reference crucible (1%) |
| technique: | temperature ramp 4 $^{\circ}$ C/min from -10 $^{\circ}$ C up to 400 $^{\circ}$ C |

Before closing the crucibles, the samples are exposed to an oxygen atmosphere in a glovebox. Experiments performed in the laboratory show that an exposure time of 5 min is sufficient to saturate the crucible atmosphere with oxygen. Moreover, the sample amount was reduced from ca. 5 mg to ca. 0.5 mg to increase the oxygen volume/sample amount ratio in the crucible. This last point is not essential, but it will increase the effect of the influence of oxygen on the thermal stability of the investigated substances.

The tests performed under oxygen atmosphere show very highly exothermal decomposition reactions if the samples are sensitive to an air flow according to the RADEX experiments. The obtained results are comparable in both cases.

The thermogram of the Polysynthren blue dye in the presence of oxygen is shown in the Figure 12. An important decomposition reaction starting at ca. 260 $^{\circ}$ C is observed (about -1680 kJ/kg). The effect of oxygen is clearly determined in comparison with the test performed under argon atmosphere (see Figure 5). The same effect is observed during the RADEX tests performed with open tubes (see Figure 7). However, the measured decomposition energy depends on the oxygen amount in the crucible.

Indeed, the energy measured in the DSC oven corresponds to a small part of the heat of combustion of the investigated substances. For example, the heat of combustion of the Polysynthren blue dye determined with a Framo MK2 combustion calorimeter is about -35100 kJ/kg. The energy measured during the DSC experiment under oxygen atmosphere corresponds to ca. 5% of the whole heat of combustion. The scheme of the combustion reaction shows that 40.5 mol pure oxygen are required for the complete combustion of one mole of this compound. The calculation of the oxygen volume in the testing vessel shows that 5% of the necessary gas amount is available if 0.5 mg of substance is utilized (see Figure 12). If the sample amount is increased by a factor 2, the energy per sample unit mass measured during the DSC test under oxygen atmosphere is halved.

The same comparison between the energy measured during the DSC experiment under oxygen atmosphere and with the combustion calorimeter was done for the other substances. It shows a good correlation between the available oxygen amount in the DSC crucible and the part of the heat of combustion measured.

In the case of substances which are not sensitive to an air flow according to the RADEX experiments, the same

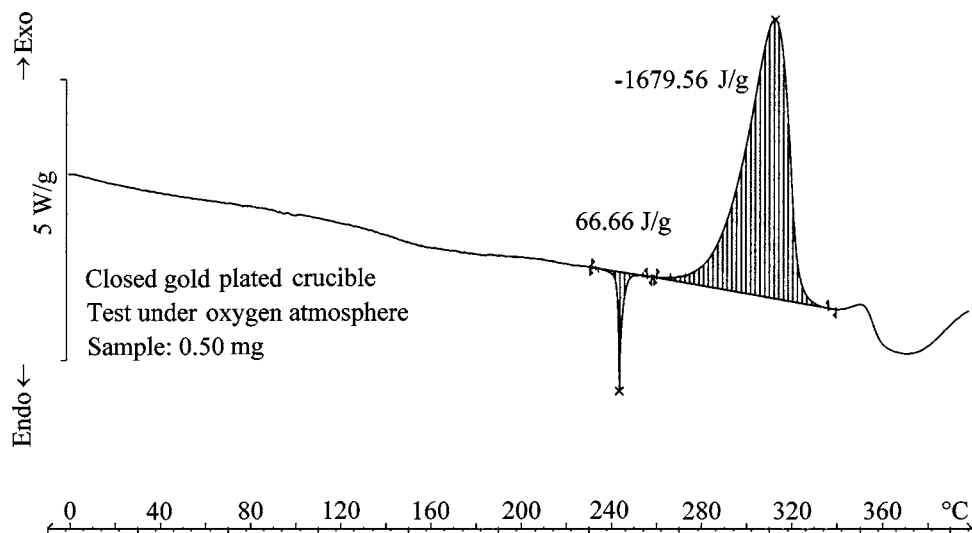


Figure 12. Dynamic DSC thermostability test under oxygen atmosphere (Polysynthren blue dye).

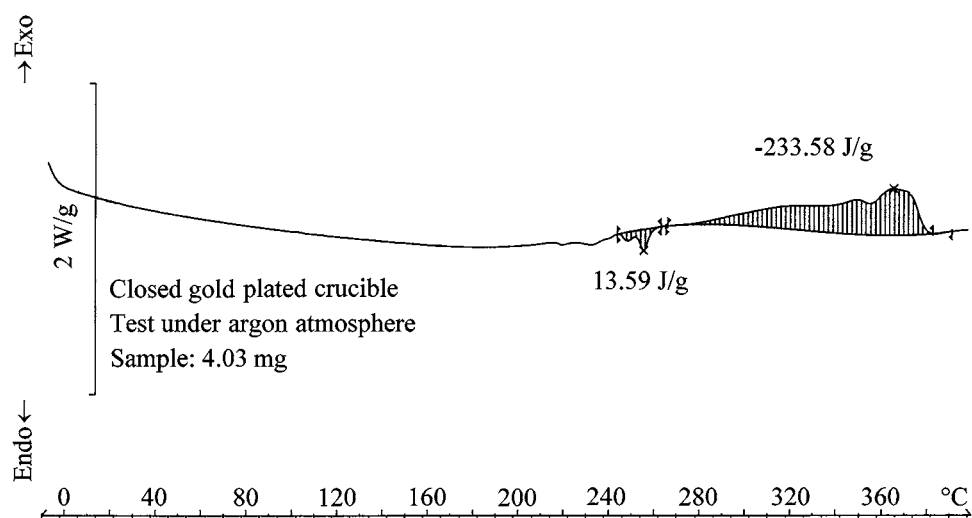


Figure 13. Dynamic DSC thermostability test under argon atmosphere (Carta F Yellow G PRD dye).

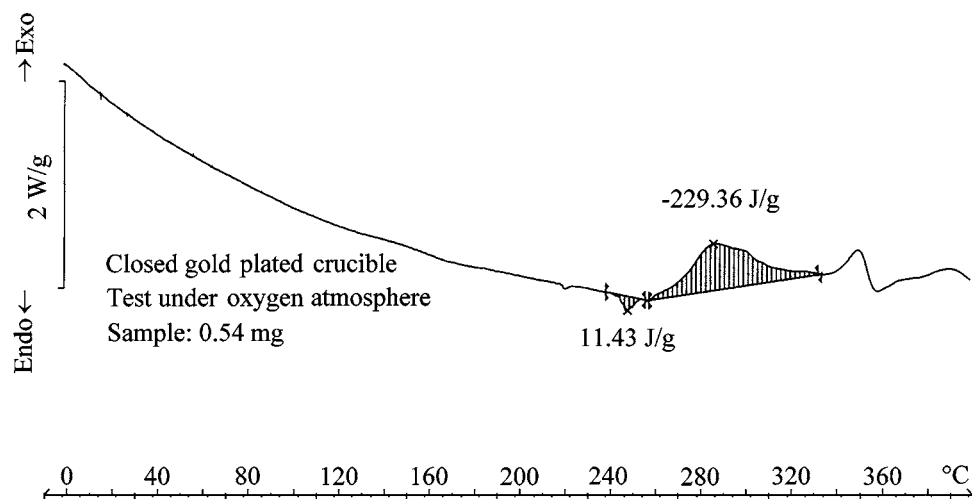


Figure 14. Dynamic DSC thermostability test under oxygen atmosphere (Carta F Yellow G PRD dye).

conclusions can be drawn using closed DSC crucibles under argon and oxygen atmospheres (see Figures 13 and 14; Carta F Yellow G PRD dye). Comparable decomposition energies were measured in both cases.

These methods combining two DSC experiments performed with closed crucibles can be used instead of the RADEX tests using open testing vessels. The influence of the entry of an air flow on the thermal stability of the

investigated substances can reliably be determined. The information obtained with these DSC tests can be used during risk analyses to define adequate process conditions and necessary safety measures.

Moreover, the duration of the experiments is much shorter than using the high-pressure DSC device (test under air pressure). Standard DSC apparatus with sample robots can be used to increase the productivity of the testing laboratory.

Furthermore, as these tests are performed with closed crucibles, no emission of toxic decomposition compounds can occur, leading to an optimal process from the hygiene and environmental point of view.

Samples must be representative of the material which is handled in the pilot plant or in production. In the case of macroscopic heterogeneity of a material it is recommended to perform tests with several samples. In case of a large variance of the results, tests should be repeated using the traditional methods which are more appropriate for heterogeneous compounds due to the larger sample amount. Nevertheless, the laboratory operator may be exposed to potential degradation compounds during the completion of the tests and the cleaning of the testing device.

Further isothermal thermostability tests must generally be performed to detect delayed decompositions (sometimes called autocatalytic reactions) and thus determine the maximum admissible working temperature.

Additional tests are also necessary to assess the safety of unit operations for drying (combustibility test, falling-hammer test, dust explosion test, etc.). The required safety measures are generally summarized in internal guidelines or recommendations of the pharmaceutical or chemical com-

panies. Differences can occur due to specific plant equipment and to the divergence of safety standards between each company. Generally, a given temperature difference between the onset temperature of an exothermal decomposition reaction in the presence or in absence of air is the main criterion (30 °C in our case). The ratio between the heat of decomposition measured under inert conditions and in the presence of oxygen can also be used.

Conclusions

A new method for the assessment of the influence of an air flow on the thermal stability of powders is proposed and discussed. This method, based on DSC experiments performed with closed crucibles in the presence of oxygen, leads to significant improvements of the working conditions from a hygiene and environmental point of view (no exposure to toxic decomposition compounds, no gas release into the environment). Moreover, the small sample amounts required for testing lead to a cost reduction for some very expensive pharmaceutical substances.

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