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Detection of previously unknown menthol polymorphs by Flash DSC

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Knowledge of the polymorphic forms of an active substance is very important, especially in the pharmaceutical industry. In this article, we show how previously unknown polymorphs of menthol can be identified and characterized by Flash DSC.

Introduction

Both the stability of a chemical compound and its solubility in a medium depend on the structure of the compound. For example, in the development of a pharmaceutical substance it is important to identify different polymorphs and assess their stability. DSC is often used for the rapid detection of polymorphs.

Here the choice of the heating and cooling rate has a large influence on whether polymorphs are found and if so which ones. The formation of a structure in a liquid is strongly influenced by the cooling conditions. Depending on the cooling rate, different polymorphs or mixtures of different polymorphs are formed. During heating, reorganization processes occur which indicate the presence of other polymorphs.

Conventional DSC instruments provide heating and cooling rates of up to a maximum of about 300 K/min. In this article, we show how the high heating and cooling rates possible in the Flash DSC allow polymorphs to be identified that cannot be detected by conventional DSC. The substance chosen for this work was menthol. Previously unknown polymorphs were found both in levorotatory levomenthol as well as in the racemate (a 1:1 mixture of levorotatory and dextrorotatory enantiomers).

Experimental details

Levomenthol or (1R,2S,5R)-5-methyl-2-propan-2-yl cyclohexanol) was obtained from the Acros Organics company and the racemate from Alfa Aesar in the form stable at room temperature and normal pressure (the α -form). The measurements were performed using a METTLER TOLEDO Flash DSC 1. Heating and cooling rates of 1000 K/s were used. A single crystallite was positioned on the sensor for the measurements.

The mass of the crystallite used for the Flash DSC measurement m_{FDSC} cannot be directly determined. It can however be estimated by comparing the enthalpy of fusion of the α -form, ΔH_{FDSC} (in μJ) measured in the Flash DSC measurement with the enthalpy of fusion of the stable form normalized with respect to mass measured by conventional DSC (Δh_{α} in J/g), according to eq 1:

$$m_{\text{FDSC}}[\mu\text{g}] = \frac{\Delta H_{\text{FDSC}}}{\Delta h_{\alpha}} \quad (1)$$

Results and discussion

Figure 1 shows the first and second heating runs and cooling run of a sample of levomenthol at 1000 K/s. In the first heating run, there is an endothermic melting peak at about 51 °C (onset). Conventional DSC measurements show that α -levomenthol melts at 42.9 ± 0.3 °C [1–4].

The large difference between the onset temperature of the melting peak in the first Flash DSC measurement and the literature value is a result of the poor thermal contact between the sample and the sensor in the first heating run. Thermal contact with the sensor is only well-defined after the sample has melted the first time.

After the first heating run, the sample was cooled at 1000 K/s. At this high cooling rate, the sample cannot completely crystallize. At $-60\text{ }^{\circ}\text{C}$, it is present as a semicrystalline material. The second heating run therefore shows a glass transition at about $-27\text{ }^{\circ}\text{C}$. Besides this, there is a cold crystallization process at about $-2\text{ }^{\circ}\text{C}$.

Melting begins at about $32.8\text{ }^{\circ}\text{C}$. This temperature is appreciably lower than the melting point of α -levomenthol ($42.9 \pm 0.3\text{ }^{\circ}\text{C}$) and is also lower than the melting point of metastable β -levomenthol ($35.3 \pm 0.3\text{ }^{\circ}\text{C}$ [1]). It must therefore be due to another metastable phase. In fact, in the literature there is information about a second metastable form (γ -form) that melts at about $33.5\text{ }^{\circ}\text{C}$ [2].

The mass of the sample measured in the Flash DSC can be estimated from the enthalpy of fusion of the α -form (14.1 kJ/mol or 90.1 J/g). According to eq 1 the mass is about 145 ng . In addition, the enthalpy of fusion of the presumed γ -form, Δh_{γ} , can be determined from the data in Figure 1 as follows:

$$\Delta h_{\gamma} = 11.13 \text{ } \mu\text{J} \cdot 14.1 \text{ kJ/mol} = 6.3 \text{ kJ/mol}$$

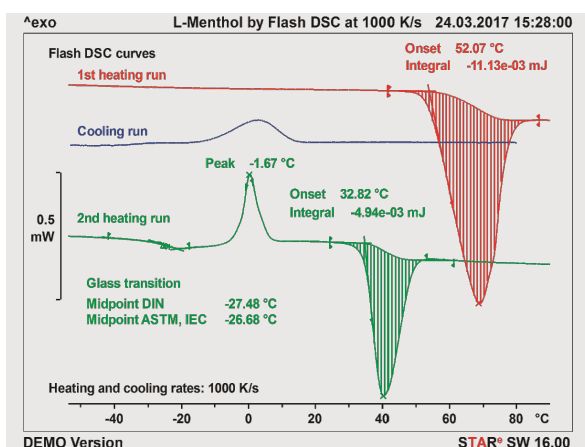


Figure 1 Heating-cooling-heating measurement of levomenthol at 1000 K/s. For details, see text.

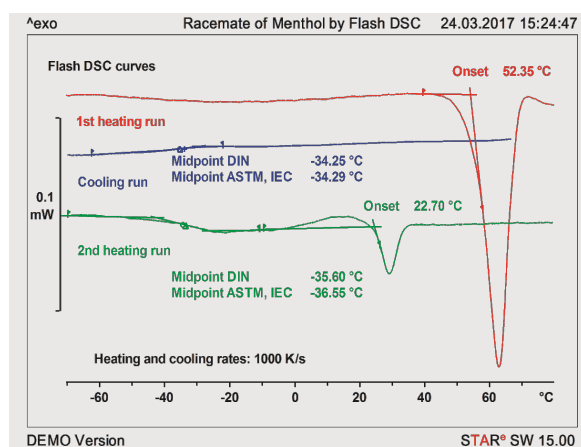


Figure 2 Heating-cooling-heating measurement of the racemate of menthol at 1000 K/s. For details, see text).

The enthalpy of fusion estimated for the γ -form is markedly lower than the enthalpy of fusion of the β -form (11 kJ/mol). This indicates that the high heating and cooling rates possible with the Flash DSC enabled a polymorph of levomenthol to be found that cannot be detected by conventional DSC.

The polymorphism of racemates of menthol was first investigated experimentally using conventional DSC and XRD [1]. In this work, the existence of a metastable β -form (also called pseudoracemate 2) was reported that melted at $27.3\text{ }^{\circ}\text{C}$. On the basis of model calculations, a further pseudoracemate (pseudoracemate 1) was predicted that should melt at $23.2\text{ }^{\circ}\text{C}$. Up until now, this polymorphic form has not been found experimentally.

Figure 2 displays measurement curves of the racemate of menthol recorded with the Flash DSC. The diagram shows the first and second heating runs and the cooling run in between. During the first heating run, the stable α -form melts. The cooling rate (1000 K/s) is so high that no crystallization occurs during cooling.

Instead, a glass transition is observed at about $-34\text{ }^{\circ}\text{C}$. During the second heating run, the glass transition is again observed at about $-36\text{ }^{\circ}\text{C}$. Cold crystallization occurs at about $10\text{ }^{\circ}\text{C}$. The crystallites that are formed melt immediately afterward and yield a melting point of about $22.7\text{ }^{\circ}\text{C}$, which agrees well the temperature of $23.2\text{ }^{\circ}\text{C}$ estimated from model calculations. This temperature is however not so exact because crystallization and melting overlap

For the same reason the enthalpy of fusion of this racemate form cannot be estimated. By means of Flash DSC, the existence of this predicted form has nevertheless been detected experimentally for the first time [5].

Conclusions

Experiments are usually performed at different heating and cooling rates in order to investigate polymorphic behavior. Whether a particular form occurs depends greatly on the heating and cooling conditions. Using levomenthol and a racemic sample of menthol, we showed that unknown polymorphs could be found with the aid of the Flash DSC and its high heating and cooling rates.

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