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USE OF SUBAMBIENT DSC FOR LIQUID AND SEMI SOLID DOSAGE FORMS
Pharmaceutical product development and quality control

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Abstract

Examples of the use of subambient DSC for characterizing excipients which have the melting range within ambient or subambient temperatures as well as liquid and semiliquid dosage forms are presented in the following paper.

Influences of the quality, polymorphism, storage of excipients used for dosage forms and changes in the composition on the melting behaviour and quality of dosage forms were investigated.

Changes of the melting behaviour of dosage forms determined with subambient DSC have shown to correlate with the quality of the dosage form, the quality of excipients used or structural changes (due to various influences) in the dosage form. DSC for use in the range of subambient and ambient temperatures represents an alternative analytical method for development and quality assurance in pharmaceutical industry for liquid and semiliquid preparations.

Keywords: liquid preparations, physical characterization, quality assurance of dosage forms, semi-solid preparations, subambient DSC

Introduction

In pharmaceutical industry fast and reliable characterization and estimation of the quality of pharmaceutical preparations as support of drug development is important. Similar to solid preparations, DSC may be used for determining quality and thermal characteristics of liquid and semi-solid preparations and their single compounds as well as drug-excipient and excipient-excipient interactions [1]. Many of these transitions take place at or below room temperature. Sufficient cooling of the DSC apparatus with an adequate cooling equipment is therefore necessary. Some examples of the use of subambient and ambient DSC application on complex semisolid and liquid preparations are presented. Up to now, DSC has widely been used for measuring thermal behaviour of semi-solid and liquid preparations in combination with microscopical, rheological, X-ray diffraction and spectroscopic methods for structural investigations [2–6]. Phase behaviour of excipients with

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melting/transition points at ambient temperatures as well as interactions of drug substances with excipients were investigated [7–8]. However, the results obtained especially from investigations performed on creams or gels are used for description of the structure. Interpretations with regard to stability predictions are admittedly difficult and therefore rare [9]. The results obtained need to be complimented with other methods such as microscopical, rheological and X-ray diffraction methods. But the advantages of DSC are known: high sensitivity, fast and reliable results and low amount of substance is needed. With DSC, also phase transitions that are not obvious in thermomicroscopy are detectable. It is known that the inner structure of a formulation influences not only physical stability of a dosage form but also the amount of available drug and its release. Characterizing and understanding the microstructure of liquid or semi-solid formulations as well as their single compounds is indispensable for a scientific approach of new formulations and probable predictions of stability. Our experiments were done on complex formulations, and it must be pointed to the fact, that every excipient added to a mixture changes the formulation and its physical properties. DSC was found to represent an alternative approach for characterizing liquid and semi-liquid dosage forms.

Experimental

A DSC 7 from Perkin Elmer (Norwalk USA) equipped with Intracooler II and Drybox, Digital DEC station and Perkin Elmer thermal analysis software version 3.00 for data analysis was used. For some polymorphism investigations a DSC 2 from Perkin Elmer (Norwalk USA) with Perkin Elmer thermal analysis station with TADS DSC standard program was used. For enthalpy calibration certified Indium (purchased from the Governmental Chemistry Laboratory, Teddington, Middlesex, GB) was used. For temperature calibration certified Indium and 4-Nitrotoluene (purchased from the Governmental Chemistry Laboratory, Teddington, Middlesex, GB) were used. In DSC scans, heating rates of either 5 K min^{-1} or 10 K min^{-1} were applied. 10–30 mg of substance were sealed into tightly closed pans.

Polymorphism of excipients

Influence on quality of dosage form

Excipients perform specific technological functions in dosage forms. They are used to guide the drug release, for improving stability or simply to make the drug substance applicable. Many excipients or compounds of them used in pharmaceutical preparations show polymorphism [13–19]. This may have considerable influence on preparation and stability of the dosage form often due to different solubility of the polymorphs.

A liquid dosage form containing as excipient corn-oil glycerides has been investigated. After storage of the dosage form placebo at lower temperatures, precipitation has been observed in some samples. Finally it was found that the precipitation is correlated to the quality of corn-oil glyceride especially the content of mo-

nopalmitoylglyceride (MPG). MPG itself shows polymorphic behaviour and causes in this case problems. Using DSC the polymorphic behaviour of MPG can be monitored: MPG shows transitions at 30° (α to β') and at 40°C (melting of β'). In freshly heated solution no precipitation occurs at room temperature, during storage, MPG crystallizes in its higher melting form (β') and therefore the solution shows precipitation. When one or part of the excipients used in the preparation precipitates in the formulation, it is possible, that the drug substance could also be dragged to precipitation. Figure 1 demonstrates the problems that may occur using a compound containing too much MPG: To liquid dosage form (A), crystalline monopalmitoylglyceride (MPG) was added. MPG makes part of one particular excipi-

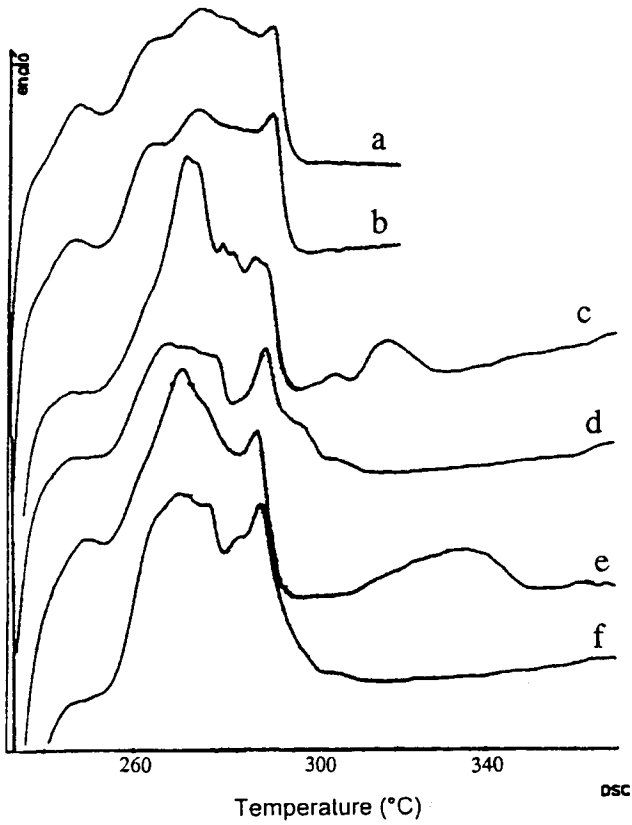

Fig. 1 a) Liquid dosage form A), first heating; b) liquid dosage form A), second heating: no polymorphism appeared; c) liquid dosage form A with addition of MPG. First heating: the crystallized MPG melts separately at higher temperature; d) liquid dosage form A with addition of MPG. Second heating: the incorporated MPG melts in its lower melting form; e) liquid dosage form A with addition of MPG. First heating after storaging (r.t./10 days): the recrystallized MPG melts again as a separated peak (endothermal peak at about 338 K); f) liquid dosage form A with addition of MPG: second heating after storage. Curve e) and f) show that MPG is transformed back to its higher melting form during storage and therefore crystallizes again

ent used in the liquid dosage form and was – together with other palmitoylglycerides – considered as to be problematic when exceeding a certain concentration in the excipient. MPG itself shows polymorphic transitions at 30° (α to β') and at 40°C (melting of β').

Quality of excipients

Influence on quality of dosage form

Interactions of excipient and excipients with drug substance may be determined with DSC and are described in literature [1, 7, 10].

Knowing the quality and the content uniformity of the excipients used is essential [11, 12] to form a good base for quality in dosage forms. With DSC, batch to batch variations, purity, actual thermodynamical state, stability, compatibility, phase transitions and crystallinity can be determined.

Excipients are often not obtainable in very pure state, especially when they are of natural origin and batch variation may be rather high. Furthermore they themselves are often mixtures of different compounds. It has been seen that the quality of the excipients, especially the content of long chain components has a significant influence to the quality of the product. The chainlength can be correlated to the melting point and usually the melting point increases with increasing chain length. Therefore, while determing the melting behaviour with DSC, a differentiation of the quality of the excipients is possible.

The melting behaviour of two batches of Cremophor RH 40 was investigated. Cremophor RH 40 consists of polyoxyethylated, hydrated castor oil as main product

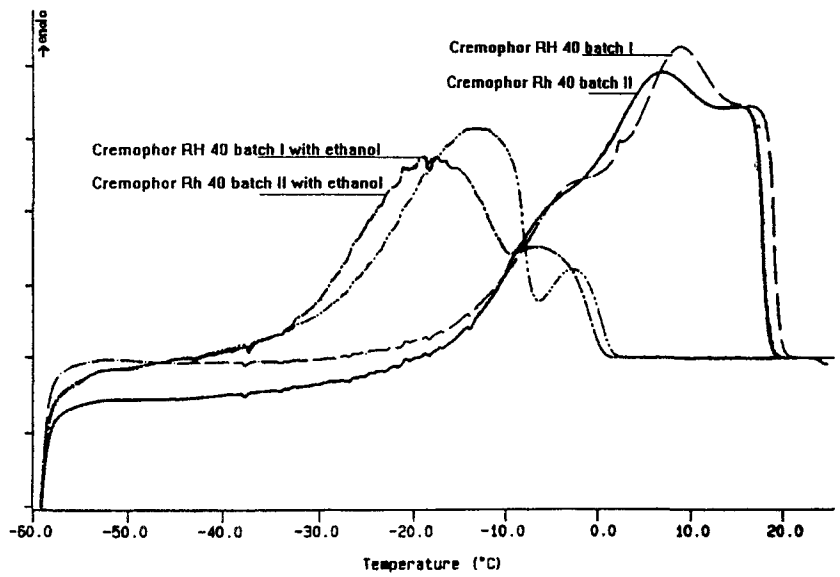

Fig. 2 The DSC curves of two cremophors RH 40 batches representing two qualities and the corresponding mixtures with ethanol are shown

and further of polyoxyethylated hydrated fatty acid esters, polyoxyethylene and polyoxyethylated glycerolethers.

In DSC significant differences between the two batches can be seen. These differences are also visible in the mixture with ethanol (Fig. 2). The differences can be correlated to the content of long chain fatty acids. The sample with the higher melting point contains more long chain fatty acids.

Optimizing dosage forms and estimation of quality as support for galenical development

Due to the short biological half-life of certain drugs, new galenical forms have to be developed to make such substances applicable [21]. In the developing of two oral solutions containing lipophile excipients, DSC was applied to determine the melting range of the composition as the solutions showed precipitation during storage at lower temperatures.

Liquid dosage forms are promising drug delivery systems for difficult applicable drug substances for oral application due to their short biological half-life. Liquid dosage forms are considered to be thermodynamically stable systems, but solidification or gelification of the excipients may occur at lower storage temperatures. Although these solidifications are reversible when the preparations are heated up to ambient temperature, the aspect of the solutions regarding the patients' compliance should be considered. With DSC the temperature range where the formulation shows no precipitation can be determined.

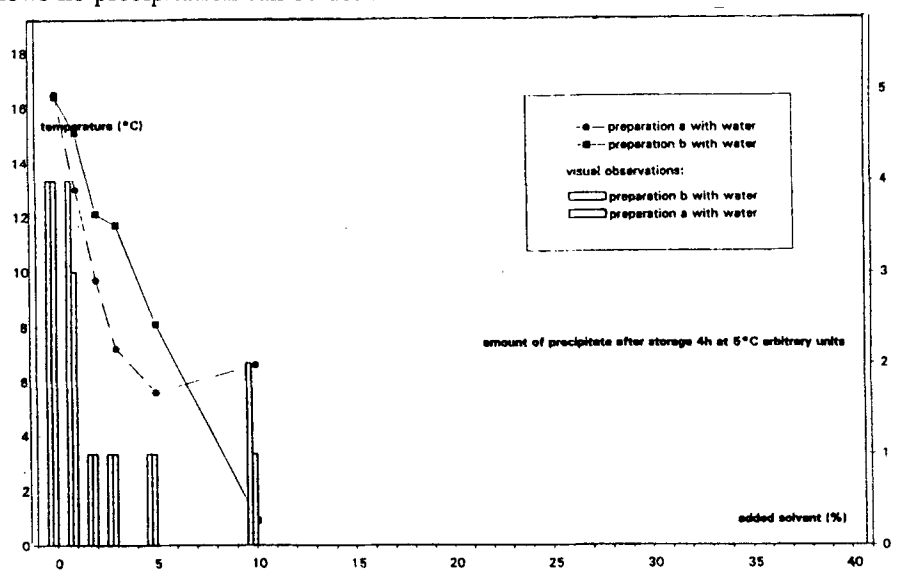

Fig. 3 Comparison between visual observation and DSC measurements, preparation a and b with water

The oral solutions (a and b) investigated differ in one of the lipophilic excipients. To both preparations ethanol (10–40%), water (1%, 2%, 3%, 5%, 10%) and mixtures of water and ethanol (5%/10%, 10%/10%) were added. The melting behaviour was observed with DSC. In parallel, the preparations were stored in the refrigerator and the forming of precipitates was observed visually. The aim was to find a correlation between the forming of precipitates at the chosen storage temperature (5°C) and storage time and the melting temperature in DSC. While in preparation (b) (Figs 3 and 4) a continuous lowering of the melting temperatures was reached with further addition of either water or ethanol, the addition of 10% water to preparation a gave worse results and the addition of a certain amount of ethanol did not lead to further amelioration.

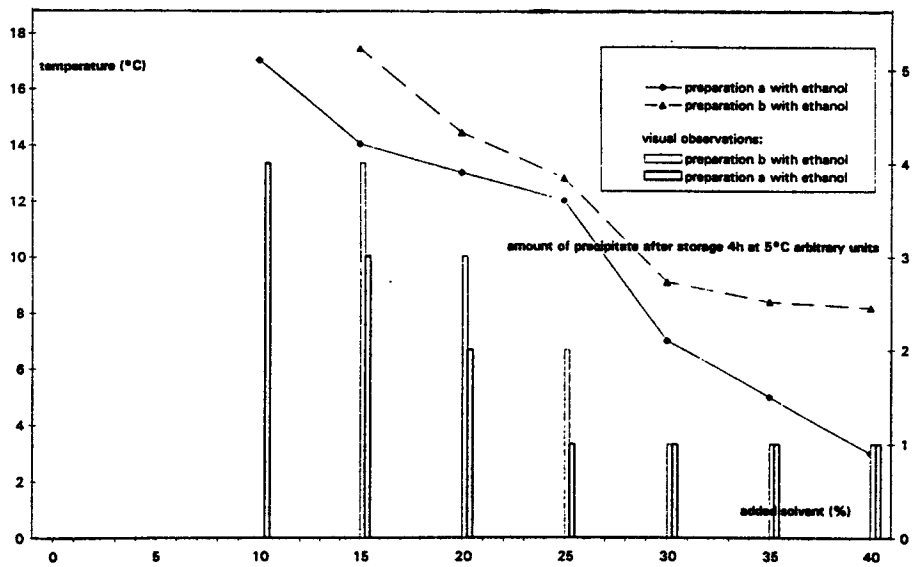

Fig. 4 Comparison between visual observation and DSC measurements,preparation a and b with ethanol

From the change of the melting curve it can be assumed further, that the addition of 10% water to liquid dosage form (a) leads to a phase change, while in liquid dosage form (b) the addition of the same amount of water did not lead to any phase change. In the storage at 5°C, preparation (b) with high amount of water showed better stability than preparation (a).

Investigations on dermal formulations with DSC

Semisolid preparations such as creams are thermodynamic unstable systems. Depending on the excipients used they show a large variety of their microstructure: they can form different phases such as e.g. cubic, lamellar, hexagonal phases or others such as (micro)-emulsions or hydrogels built of hydrophilic polymers. De-

pending on temperature and water content, they occur in different states, e.g. in gel phase or liquid crystal phase [22, 23]. Small changes in composition or purity of chosen excipients may influence the inner structure of the dermal formulation [24–26]. In DSC, structured preparations show a specific DSC pattern and their changes can be registered [27, 28]. DSC experiments can supply informations about behaviour and interactions of the excipients (emulsifiers, oil phase) of creams.

O/w structures can be described with the following scheme [29] (Fig. 5).

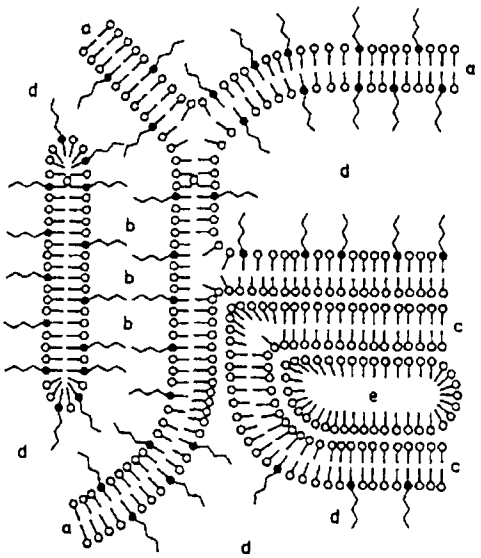

Fig. 5 a) lipophil/hydrophile emulsifier; b) interlamellarily bound water; a)+b) form the hydrophile, three-dimensional, continuous gel phase; c) crystallized emulsifier; d) bulk water; e) disperse lipophile phase

Depending on the composition (structure building substances, content of water) and/or temperature, these structures can change, and the temperature of any phase transitions may lie in ambient/subambient temperature range. The effect of different external influences was observed with DSC: Aging, shear stress, loss of water and storage at different temperatures was observed. Aging of a cream may be due to changes in the structure as well (Fig. 6): A formulation with known instability containing glycerolmonostearate as main emulsifier was chosen to follow any changes in DSC.

Changes in composition:

Water plays an important role in cream formulation and building up of creamstructures: Water can be bound interlamellarily, while the amount of water bound depends from the structure giving substances. A changed water content leads to structural changes and to changes in the DSC pattern (Fig. 7). Loss of water may lead to collapse of cream structures. An o/w formulation was stored at different relative humidities and DSC curve was registered after storage (Fig. 8). The measurements

indicate, that only beyond 98% r.h., loss of water was not important and the structure remained intact.

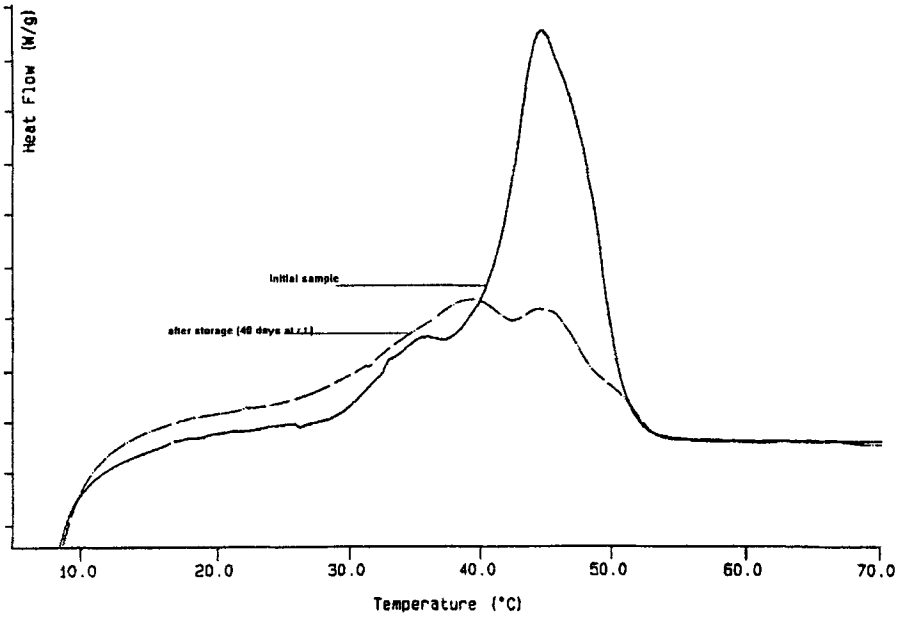

Fig. 6 Aging of a cream containing glycerolmonostearate: The DSC curves of the initial sample and after storage for 40 days at room temperature

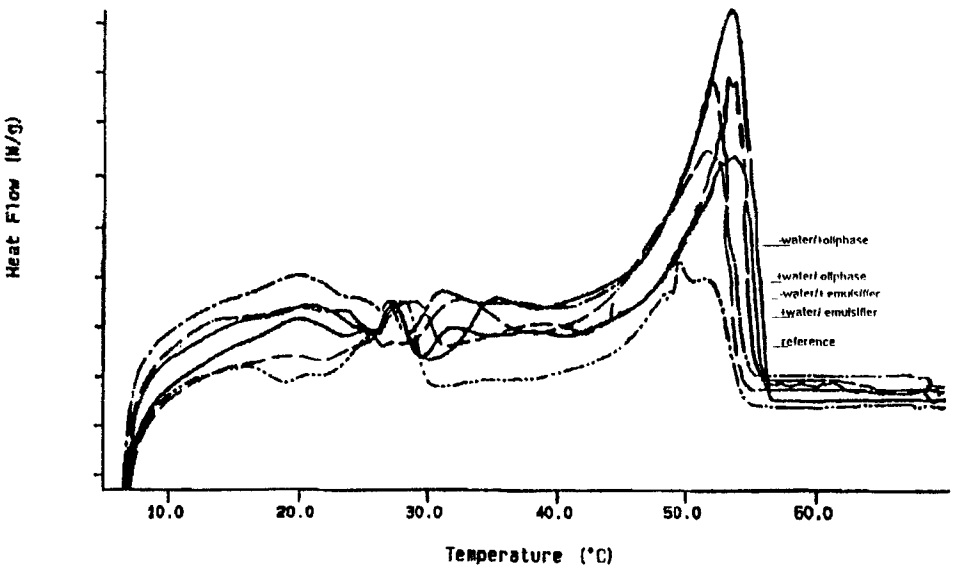

Fig. 7 Changes in DSC curves due to changes of the inner structure (structure building substances were added or left out)

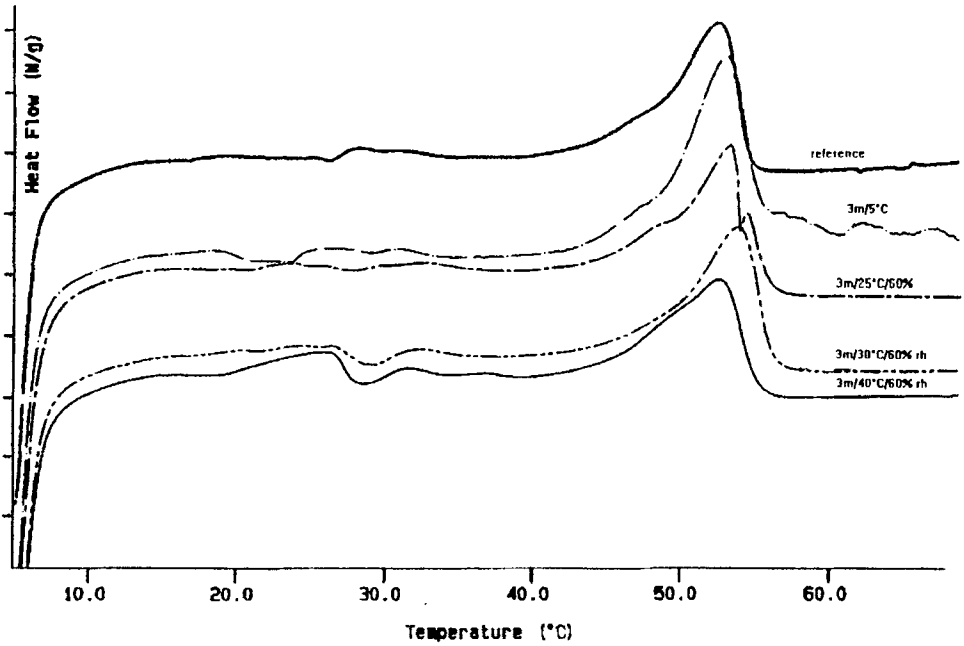

Fig. 8 Influence of storage: The formulation was stored at different temperatures. With DSC, changes could be seen after 3 months storage at 30 and 40°C respectively

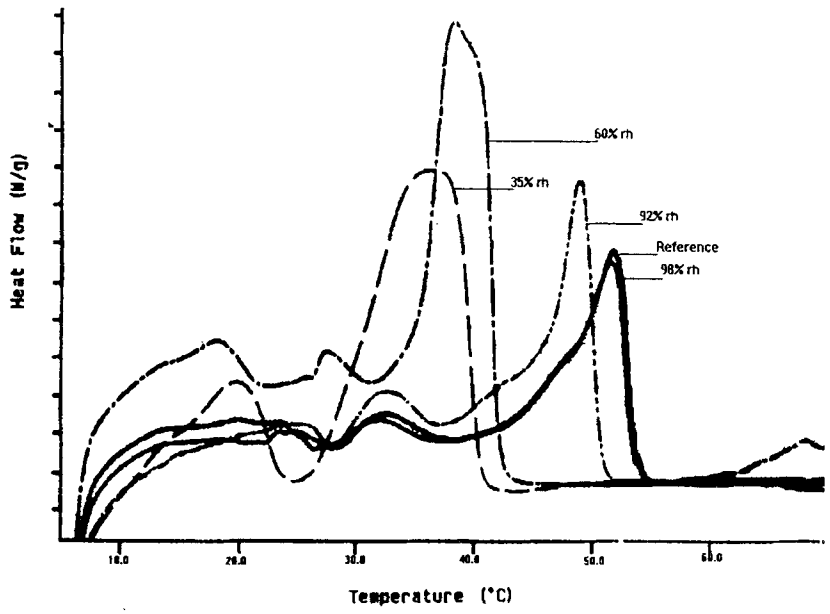

Fig. 9 O/W formulations stored under different relative humidities

Two formulations were investigated, a shearstress-sensitive and non-sensitive o/w cream formulation. Shearstress was applied to both formulations and DSC was registered immediately after applying shearstress. Figure 10a shows the non-sensitive o/w cream formulation and Fig. 10b shows the shearstress-sensitive o/w formulation.

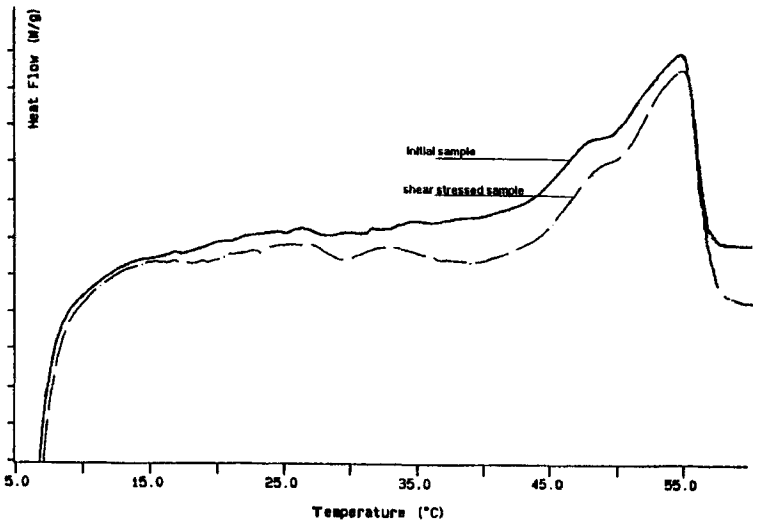

Fig. 10a Non-sensitive o/w-cream formulation

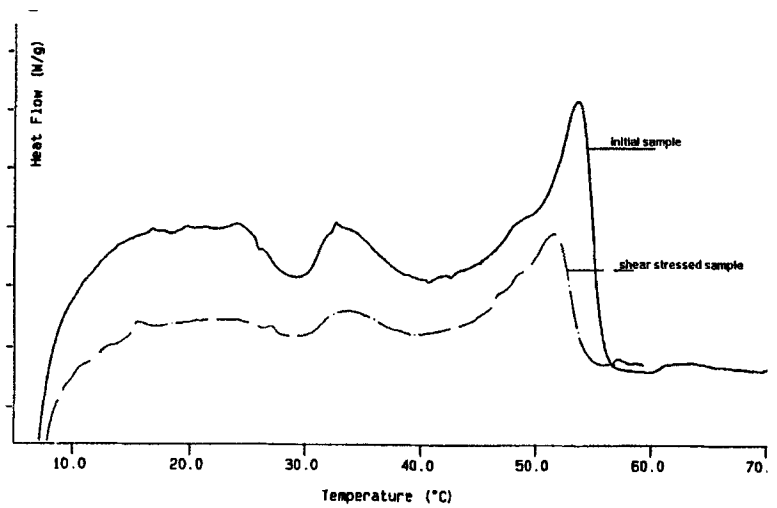

Fig. 10b Shear stress-sensitive o/w-cream formulation

Conclusion

Examples for the characterization of excipients with low melting points at ambient/subambient temperatures using DSC have been presented. Content uniformity

and polymorphic behaviour of excipients may be determined as well as their influence on the quality of semisolid and liquid dosage forms. The results reveal, that high attention should be paid already in early development phases to purity, polymorphism, content uniformity of the excipients used as well as to excipient-excipient and excipient-drug substance interactions.

Changes of the melting behaviour of semiliquid and liquid formulations determined with subambient DSC correlate with quality of excipients, changes in polymorph of excipients or structural changes in formulations.

The interpretation especially for complex preparations of creams and ointments used for commercial products is still difficult and from the actual results predictions about stability also with complementary methods (Microscopy, SAXRD) can not be made so far. DSC at subambient/ambient temperatures is a helpful tool in development and quality assurance in pharmaceutical industry for liquid and semiliquid preparations and its applications should be extended.

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