ELSEVIER

Thermochimica Acta 367–368 (2001) 37–41

thermochimica acta

www.elsevier.com/locate/tca

Thermally stimulated currents observed in pharmaceutical products

Marc Galop*, George L. Collins

TherMold Partners, Stamford, CT 06905, USA

Received 24 September 1999; accepted 16 May 2000

Abstract

Stability and processing of pharmaceutical products are often related to the molecular mobility of the formulation. It is crucial to know all the transitions or relaxations of the products. Differential scanning calorimetry (DSC) measurements give valuable information about the melt of the substances. The challenge is actually to detect very weak glass transitions and even beta relaxations. The aim of this presentation is to show that thermally stimulated current (TSC) is a driven technique that provides a better sensitivity to glass transition and sub-glass relaxations. TSC was applied to the evaluation of the stress in tablets and on the measurement of low amorphous content (in the order of 2%). TSC complements DSC to obtain the relaxation/transition ''spectrum'' of a pharmaceutical product.

Keywords: Pharmaceutical products; Differential scanning calorimetry; Thermally stimulated current

1. Introduction

Many pharmaceutical products are presented to patients in solid state forms. Even formulations for injections are often stored as powders. Therefore, stability, dissolution rate, or drug activity of the final product are correlated to the physical property of the pharmaceutical. In particular, there is need to characterize the amorphous state of the different components of the formulation.

Raw materials are usually highly crystalline, but processes such as micronization may convert some crystalline material to the undesirable amorphous phase. It is important to be able to detect the presence of amorphous material. Paradoxically, conventional techniques used for detection of amorphism such as X-ray diffraction (XRD) or differential scanning calorimetry (DSC) are sensitive to the crystalline material. The object of the paper is to present an amorphous sensitive technique to investigate amorphous materials. Thermally stimulated current (TSC) was introduced by Bucci and Fieschi [1], and since then it was applied in many different fields [2]. As driven technique, the TSC response of a material is proportional to the stimulus. A glass transition is characterized by heat capacity changes along with visco-elastic changes. Calorimetry is sensitive to the heat capacity changes, while a driven technique that applies a stimulus (electrical or mechanical) is sensitive to the visco-elastic changes.

The main objective of this presentation shows that TSC completes DSC to produce the relaxations/transitions ''map'' of a drug substance. The second objective is to show a unique way to quantify the amount of stress stored in a pharmaceutical tablet.

* Corresponding author.
E-mail address: gcollins@thermoldlp.com (G.L. Collins).

0040-6031/01/$ – see front matter
PII: S0040-6031(00)00700-0

2. Experimental

We have investigated different pharmaceuticals presented in several forms; powders, tablets, or lyophilized. The powder was hand-pressed in a pellet press to create a 0.7 mm diameter flat disc. The thickness of the disc was about 1 mm. Tablets were studied with no sample preparation. For the crystallinity study, calibration samples were prepared by geometric dilution [3]. Powders of "100% crystalline phase" and of "100% amorphous phase" were blended in a Turbula blender to produce 75/25, 95/5, and 98/2 blends (crystalline/amorphous ratios).

TSC experiments were conducted with a TSC/RMA Model 9000 from TherMold Partners (Stamford, CT). Typically, the temperature of the sample was raised above the glass-transition area, where a DC electrical field (100 V/mm) was applied. Because of the molecular mobility, some dipoles are able to align in the direction of the field. By cooling the material to lower temperature, the molecular mobility is reduced to a point where the aligned dipoles cannot relax to their original position even if the field is cut off. A very sensitive ammeter is then connected to the sample to collect any depolarization current. The depolarization is induced or stimulated by a linear heating ramp at 7°C/min.

To study the relaxation of stress in tablets, no electrical excitation was necessary. The samples were heated from room temperature to above the glass-transition temperature in a passive mode. The spontaneous depolarization current was measured as the stress relaxation occurs.

3. Results and discussion

3.1. Measurement of amorphous content

Recently, TSC was applied by Boutonnet Fagegaltier et al. [4] to measure amorphous content in a pharmaceutical product. Their TSC spectrum shows three relaxation modes at low temperature in particular in the presence of crystalline material. These relaxation modes take place in the crystal itself. Unfortunately with our formulation, the crystal phase did not have any observable relaxation modes. We had to adopt a more systematic approach by studying directly the relaxation mode associated with the glass transition.

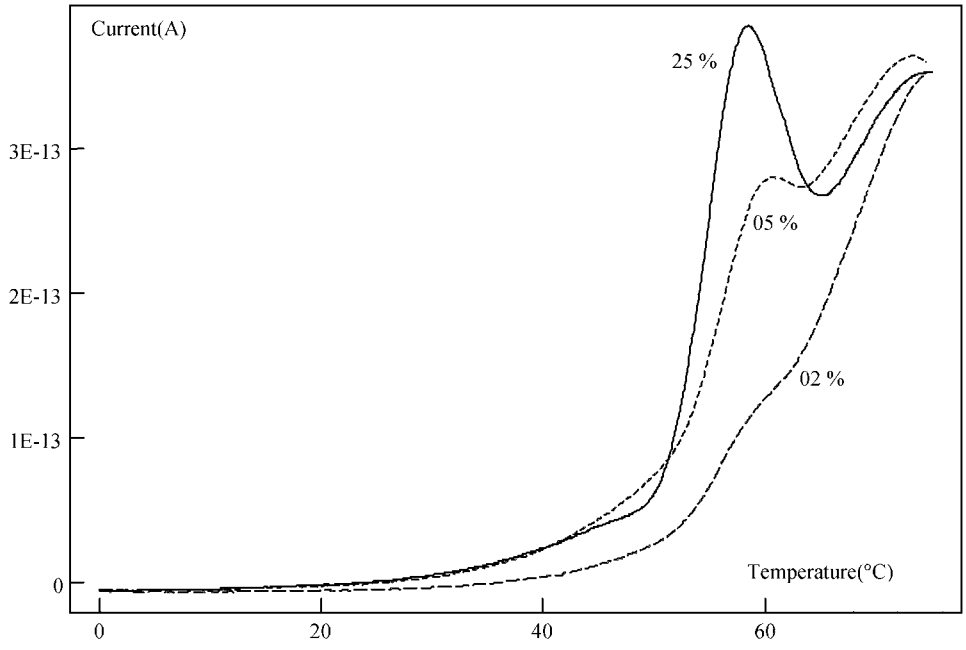

Fig. 1. Effect of the amorphous content on the TSC spectrum: 25, 5, and 2% amorphous samples.

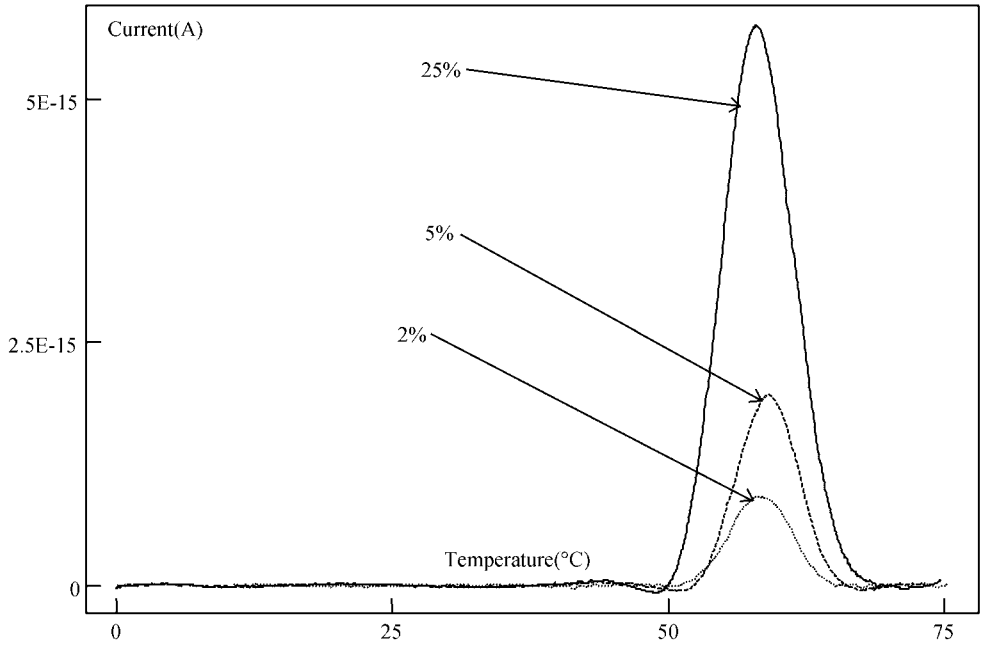

Fig. 2. Normalization of the curves of Fig. 1 (subtraction of base line + normalization by the mass).

Fig. 1 shows the TSC spectra of three blends, 75/25, 95/5, and 98/2. The two numbers refer to the crystalline/amorphous ratio. A main thermal event at around 60°C can be detected. TSC and DSC studies of the pure amorphous drug have shown that this thermal event is the dielectric relaxation associated with the glass transition. Fig. 1 displays also an overlapping process in the form of a second peak occurring at higher temperature. This peak is called a polarization peak and corresponds to the low temperature contribution of a higher temperature event.

It is very encouraging for the pharmaceutical processing industry that 2% of amorphous material can be detected. The quantification of amorphous content cannot be done by a simple calculation of the area under the curve because of the overlapping process that creates a larger error as the amorphous content diminishes. To the best of our knowledge, the polarization peak was not studied because it is often considered as a nuisance. Therefore empirical models were used to subtract the effect of the polarization peak. The approach was to consider that the glass-transition relaxation occurs in a given range of temperature. TSC study of the glass transition of purely amorphous drug has shown that the glass-transition relaxation mode only occurs between 45 and 65°C. We then subtract from the TSC curve a fitted polynomial curve (degree higher than 6) using the data outside the 45–65°C window. The resulting curve is then divided by the mass of the sample to normalize any effect due to powder packing differences. The normalized curves are presented in Fig. 2. After subtraction and normalization of the TSC curves, we can calculate the area under the curve. Fig. 3 shows the evolution of the area under the curve vs. the percentage of amorphous material.

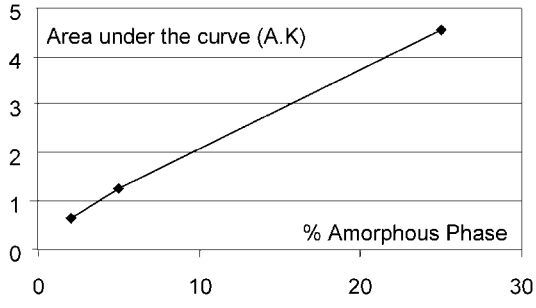

Fig. 3. Area under TSC curve vs. percentage amorphous.

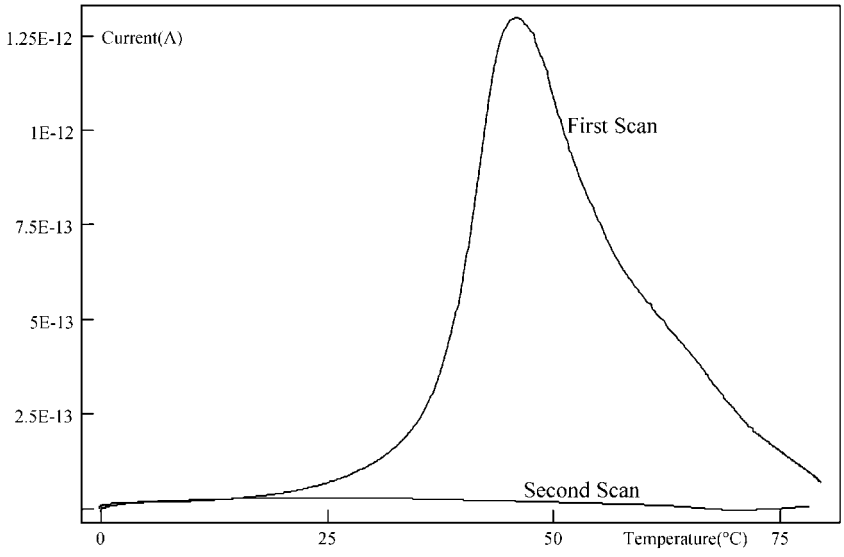

Fig. 4. Stress relaxation in tablets (first and second scan).

3.2. Internal stress in tablets

During fabrication of the tablet, some stress is trapped in the molecular structure of the compressed powder. This stress can be released later in the life of the product, in particular if the storage temperature or humidity is increased. If stress relaxation occurs, it is not unusual to observe a crack in the tablet. Quantitative estimation of stress in polymer molded parts was previously reported [5]. The principle is to induce

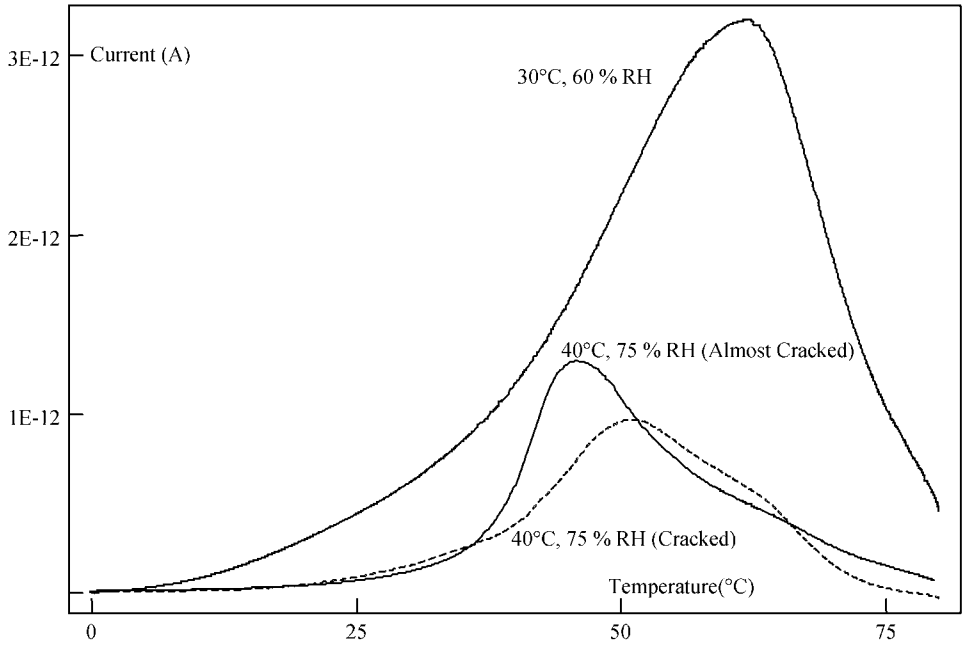

Fig. 5. Effect of storage conditions.

intentionally stress relaxation with a heating profile. The tablet is placed between the electrodes of the TSC apparatus. As the temperature increases, molecular mobility increases and induces stress relaxation. As the molecules relax, the dipoles attached to them trace their movements. The spontaneous current measured shown in Fig. 4 during the first scan reflects the motion of these dipoles as the molecules relax. To validate the measurement, a second scan on the same sample shows a relatively flat curve because there is no more stress in the tablet.

An application of this measurement is the evaluation of storage conditions for the stability of tablets. Tablets from two different storage conditions were analyzed using the previous protocol. Tablets stored at 30°C, 60% relative humidity (RH) were considered to be in good condition. Tablets stored at 40°C, 75% RH are cracked (80% of them) and obviously failed the storage test. Fig. 5 shows the stress relaxation for the different tablets, 30°C/60% RH, 40°C/75% RH cracked, and 40°C/75% RH non-cracked.

We can see that the tablets stored at 30°C/60% RH have around four times more stress than the tablets stored at 40°C/75% RH. The stress was relaxed during storage causing the tablets stored at 40°C/75% RH to crack. We can see that even the non-cracked tablets from the second batch were almost ready to crack.

4. Conclusion

Study of highly crystalline pharmaceutical products has shown the potential of TSC to observe low amorphous content (1–2%). Some work has to done to finalize the data manipulation. TSC has proven to be a unique technique to measure quantitatively stress in tablets. TSC is a perfect companion to conventional techniques such as XRD or DSC to fully observe transitions and relaxations in solid state pharmaceuticals.

References

[1] C. Bucci, R. Fieschi, Phys. Rev. Lett. 12 (1964) 16–19.
[2] C. Lavergne, C. Lacabanne, IEEE Elect. Insu. Mag. 9 (1993) 5–21.
[3] G.M. Venkatesh, C. Owusu-Fordjour, M. Galop, H.L. Brown, in: Proceedings of the AAPS Annual Meeting, San Francisco, CA, 1998, p. 315.
[4] N. Boutonnet Fagegaltier, A. Lamure, C. Lacabanne, A. Caron, H. Mifsud, M. Bauer, in press.
[5] M. Galop, Therm. Anal. 49 (1997) 107–114.