Journal of Thermal Analysis, Vol. 48 (1997) 459-464

THERMAL ANALYSIS OF AMORPHOUS PHASE IN A PHARMACEUTICAL DRUG

N. Fagegaltier[1], *A. Lamure*[1*], *C. Lacabanne*[1], *A. Caron*[2], *H. Mifsud*[3] *and M. Bauer*[3]

[1]Polymer Physic Laboratory, Paul Sabatier University, 31062 Toulouse Cédex
[2]Sanofi Research, 34000 Montpellier
[3]Sanofi Research, 31036 Toulouse Cédex, France

Abstract

Thermally Stimulated Current (TSC) spectroscopy and Differential Scanning Calorimetry (DSC) have been applied to the characterization of the microstructure of a pharmaceutical drug.

The dielectric relaxation spectrum shows two modes located in the temperature range of the glass transition. They have been attributed to the molecular mobility in the "true amorphous phase" and in the «rigid amorphous region».

Keywords: amorphous phase, pharmaceutical drug, relaxations and transitions, Thermally Stimulated Current

Introduction

The physical state of a drug could play a major role in the feasibility, stability and bioavailability of solid dosage forms like tablets, capsules, freeze-dried products. Among others, the degree of crystallinity or amorphization has been recognized for a long time as a key parameter in this respect.

The crystalline and amorphous states of a solid drug should be deeply characterized qualitatively and quantitatively. Most of the molecules are produced with a high degree of crystallinity. Nevertheless, different handlings following the crystallization (filtration, drying, milling, etc. ...) may affect the physical integrity by creating lattice dislocations, higher degree of amorphization or modifying the surface properties. Every modification could impact on the physico-mechanical properties and consequently on the dissolution rate and drug stability for instance [1].

The amorphous phase of a powder is usually studied by differential scanning calorimetry, X-rays diffraction, calorimetry or even density measurements. From a sensitivity point of view, if these techniques show more or less limitation when the level of disorder is less than 10% [2], they give equally limited information on the molecular motions affecting the different phases.

Moreover, there is a need of new techniques allowing an in-depth structural insight in the different phases constituting the solid product. In this respect, the di-

* Author to whom all correspondence should be addressed.

0368–4466/97/ $ 5.00

John Wiley & Sons Limited
Chichester

electric spectroscopy has been recently applied to a variety of pharmaceutical systems [3–4] but it does not provide a fine analysis of the internal molecular dynamics. We described here the use of Thermal Stimulated Current (TSC) which is a dielectric spectroscopy very sensitive to molecular motion associated with glass transition [5–7].

This technique has already been utilized widely for the study of both inorganic materials (insulators, semi-conductors) and organic macromolecules (collagen or elastin) [8] but does not seem to have been applied to small organic molecules.

Material and methods

We have investigated a pulverulent drug synthesized by Sanofi Research. The drug (some tens of mg) has been compressed into flat disks of diameter 0.8 cm and thickness around 1 mm.

The TSC experiments have been performed with a Thermally Stimulated Current/Relaxation Map Analysis (TSC/RMA) spectrometer from Solomat. The sample was placed in the measurement cell between plane stainless electrodes.

Before the TSC experiments, the cell was evacuated to 10^{-5} Torr for 5 min. Then, inert helium gas is introduced and the sample is subjected to a static electric field about 335 V/mm at a temperature T_p for a time t_p (2 min) which allows the orientation of the mobile dipolar units. The temperature is then lowered to $T_0 << T_p$ where the field is cut off. The polarization recovery is induced by increasing the temperature at a linear rate (7 K min^{-1}) and the depolarization current is recorded as a function of temperature [9].

Results and discussion

TSC complex spectrum

Figure 1 shows the complex TSC spectrum of the drug obtained with a polarization temperature of 80°C. We can distinguish two modes situated at –20°C and +30°C, respectively. Their temperature position is independent from the polarization temperature: these modes are intrinsic to the material. As it will be seen later

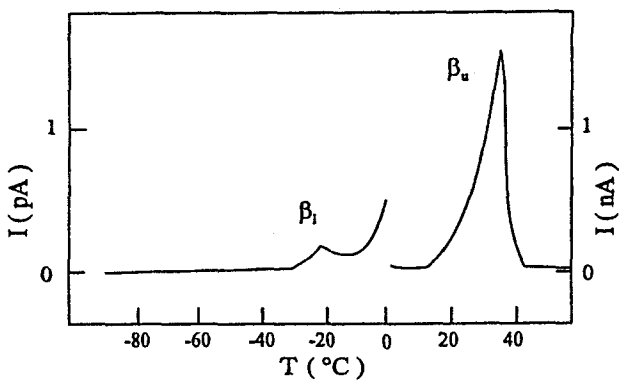

Fig. 1 TSC complex spectrum of the drug after polarization at 80°C

on, they are localized in the amorphous phase. According to the nomenclature used for semi-crystalline materials, they have been designated, respectively, as β_l (l for lower) and β_u (u for upper).

In order to characterize the origin of these modes, the fractional polarizations method has been applied.

Fine structure of TSC spectrum

The precedent TSC spectrum of the drug (Fig. 1) is complex and the fractional polarizations method [10–15] enables us to resolve it into elementary processes, and to calculate the relaxation time distribution spectrum by a subsequent analysis.

The principle is the following: the polarization is applied at a temperature T_p during a time t_p (2 min). Then the temperature is decreased to $T_d = T_p - \Delta T$ where the electrodes are short-circuited during t_d (2 min). ΔT is the polarization window (10°C). Then the temperature is decreased to $T_o << T_p$ and the increase of the temperature permits to record an elementary peak.

The polarization temperature has been shifted, respectively, by constant steps of 10°C from –60°C to –10°C for the β_l mode and by steps of 5°C from +10°C to +55°C for the β_u mode.

We obtain a set of elementary peaks whose envelope varies in the same way as the complex spectrum.

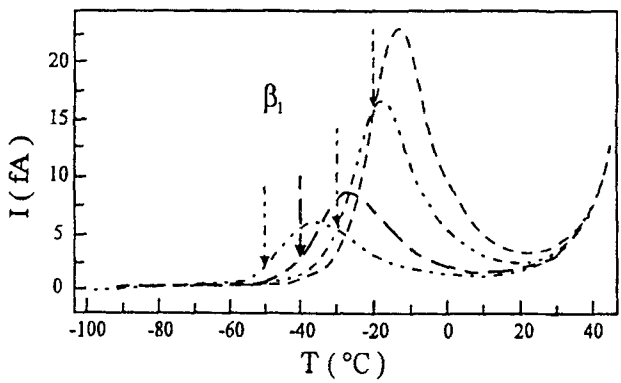

Fig. 2 Experimental resolution of TSC complex spectrum: the polarization window has been shifted by 10°C steps

For sake of clarity of the figure, we represented, on Fig. 2, the TSC spectra of processes with polarization temperature comprise between –50 and –20°C that will be seen to have a peculiar behavior.

Relaxation map analysis

The analysis of each elementary peak has been performed on the basis of the Bucci-Fieschi framework [16]. Each elementary spectrum will be described by the hypothesis of a single relaxation time $\tau_i(T)$ deduced from:

$$\tau_i(T) = \frac{P_i(T)}{j_i(T)} \tag{1}$$

where $P_i(T)$ is the remaining polarization in the sample at the temperature T, and $j_i(T)$ is the current density recorded at T.

Figure 3 shows the Arrhenius representation of the distribution of relaxation times. The experimental data obtained for each of the four elementary processes, isolated from each mode, follow a straight line. So, the corresponding relaxation times obey an Arrhenius law:

$$\tau_i(T) = \tau_{oi} \exp\frac{\Delta H_i}{kT} \tag{2}$$

where τ_{oi} is the pre-exponential factor, ΔH_i is the activation enthalpy, and k is the Boltzmann constant. The slope and the intercept of the straight lines allow to deduce the couples of Arrhenius parameters ($\Delta H_i, \tau_{oi}$).

Compensation diagram

As shown on Fig. 4, a linear relationship exists between log (τ_{oi}) and ΔH_i for several processes: the corresponding relaxation times obey a compensation law:

$$\tau_i(T) = \tau_c \exp\frac{\Delta H_i}{k}\left(\frac{1}{T} - \frac{1}{T_c}\right) \tag{3}$$

where T_c and τ_c are respectively the compensation temperature and time. The relaxation times which processes are involved in a compensation phenomenon will have the same kinetic τ_c at T_c.

These compensation parameters are the co-ordinates of the converging point of the extrapolation of the straight lines concerned (Fig. 3). A compensation phenomenon appears in the relaxation time spectrum of this drug, indicating coopera-

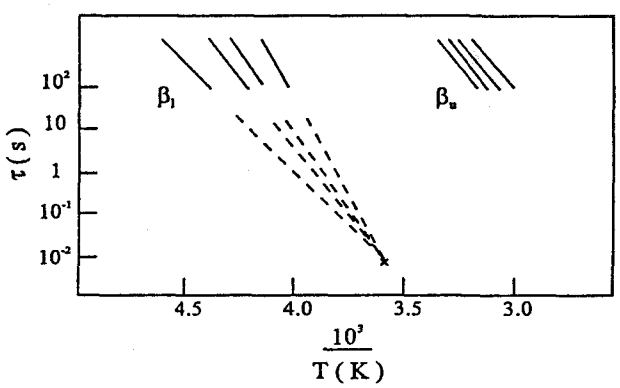

Fig. 3 Arrhenius diagram of dielectric relaxation times deduced from the analysis of the elementary peaks. Intersection occurs at compensation parameters

tive movements. It concerns the β_l mode and the compensation parameters are: $\tau_c = 7 \cdot 10^{-3}$ s and $T_c = 7$°C.

By comparing Eqs (2) and (3), the pre-exponential factors are related to the activation enthalpies by:

$$\tau_{oi} = \tau_c \exp\left(-\frac{\Delta H_i}{kT_c}\right) \tag{4}$$

Then, another representation of the compensation phenomenon is obtained by plotting in a semi-log scale the pre-exponential factors τ_{oi} *vs.* the activation enthalpies ΔH_i (Fig. 4). Indeed, when T_p increases the activation enthalpy and entropy usually increase, verifying the physical model of Hoffman-Williams-Passaglia [17]. The compensation temperature is then deduced from the slope of the straight line, and the compensation time corresponds to $\Delta H = 0$.

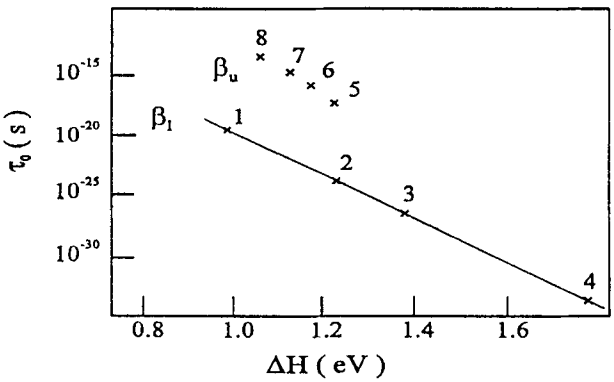

Fig. 4 Compensation diagram: pre-exponential factors *vs.* activation enthalpies: the broken line shows the compensation phenomenon

By analogy with polymers, the compensation phenomenon reveals the presence of a transition in the T_c temperature range. Complementary DSC study shows a step of heat capacity in this range temperature associated with a glass transition.

The compensation phenomenon indicates the cooperativity of the molecular movements involved in the transition. This β_l relaxation mode has been attributed to the dielectric manifestation of the glass transition of the true amorphous phase of the drug.

For the β_u relaxation, the activation enthalpies deduced from the analysis of the fine structure remain roughly constant (1.0–1.2 eV). By analogy with semi-crystalline polymers, it can be explained by a limited molecular mobility in the amorphous regions surrounding the crystalline phase. Such a relaxation phenomenon has already been observed by TSC slightly above the glass transition temperature in polymers and attributed to the amorphous regions constrained by crystallites.

High crystallinity decreases the free amorphous phase fraction (β_l) and increases the constrained amorphous phase fraction (β_u): it can explain the difference of magnitude between the β_l and β_u modes.

The existence of two modes located in the temperature range of the glass transition is often observed in synthetic or natural semi-crystalline polymers [18–21].

Conclusion

The study of a highly crystalline pharmaceutical drug by Thermally Stimulated Current has revealed the existence of amorphous domains.

Moreover, TSC analysis permitted to distinguish two types of amorphous domains having different mobilities:

– a true amorphous phase, without short range order: it corresponds to a distribution of relaxation times which obey a compensation law; there are cooperative movements. The observed difference T_c–$T_g \approx 25\,°C$ is in accordance with general observation in literature [7, 20] and depends on the crystallinity.

– a rigid amorphous phase characterized by a quasi-constant activation enthalpy: it constitutes an interphase between amorphous and crystalline phases.

It is now important to investigate how this spectroscopy could be used to study the batch-to-batch reproducibility of the drug substance and how some parameters like τ or ΔH could be used to measure quantitatively the degree of disorder of the solid drug.

References

1 G. P. Bettinetti, Il Farmaco, 48 (1988) 71.
2 P. York, Pharm. Tech. Europe, (1994) 17.
3 D. Q. M. Craig, S.T.P. Pharma Sci., 6 (1995) 421.
4 S. P. Duddu and T. D. Sokoloski, J. Pharm. Sci., 84 (1995) 773.
5 K. Yoschino, T. Sakai, Y. Yamamoto and Y. Inuishi, Jpn. J. Appl. Phys., 20 (1981) 867.
6 P. Berticat, Bui Ai, H. The Giam, D. Chatain and C. Lacabanne, Makromol. Chem., 177 (1976) 1583.
7 C. Lacabanne, A. Lamure, G. Teyssèdre, A. Bernes and M. Mourgues, J. Non Cryst. Solids, 172-174 (1994) 884.
8 C. Lavergne and C. Lacabanne, IEE Electrical Insulation Magazine, 9 (1993) 5.
9 F. Bucci and R. Fieschi, Phys. Rev. Lett., 12 (1964) 16.
10 D. Chatain, C. Lacabanne and M. Maitrot, Phys. Stat. Sol. (a), 13 (1972) 303.
11 T. Hino, Jpn. J. Appl. Phys., 12 (1973) 611.
12 D. Chatain, C. Lacabanne and P. Gauthier, J. Polym. Sci.: Polym. Phys. Ed., 11 (1973) 1631.
13 M. Zielinski and M. Kryszewski, Phys. Stat. Sol. (a), 42 (1977) 303.
14 A. L. Kovarskii, S. A. Mansimov and A. L. Buchacherko, Polym., 27 (1986) 1014.
15 C. Christodoulides, L. Apekis and P. Pissis, J. Appl. Phys., 64 (1988) 1367.
16 C. Bucci, R. Fieschi and G. Guidi, Phys. Rev., 148 (1966) 816.
17 J. D. Hoffman, G. Williams and E. Passaglia, J. Polym. Sci. C, 14 (1966) 173.
18 R. F. Boyer, J. Macromol. Sci.-Phys. B, 8 (1973) 503.
19 A. Bernes, D. Chatain, C. Lacabanne and G. Lorentz, Thermochim. Acta, 192 (1991) 155.
20 G. Teyssèdre, A. Bernes and C. Lacabanne, Thermochim. Acta, 226 (1993) 65.
21 M. Mourgues-Martin, A. Bernes and C. Lacabanne, J. Thermal Anal., 40 (1993) 697.