Molecular Mobility and Fragility in Indomethacin: A Thermally Stimulated Depolarization Current Study

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Purpose. To show that thermally stimulated depolarization currents (TSDC), which is a dielectric experimental technique relatively unknown in the pharmaceutical scientists community, is a powerful technique to study molecular mobility in pharmaceutical solids, below their glass transition temperature (T_g). Indomethacin (T_g = 42°C) is used as a model compound.

Methods. TSDC is used to isolate the individual modes of motion present in indomethacin, in the temperature range between –165°C and +60°C. From the experimental output of the TSDC experiments, the kinetic parameters associated with the different relaxational modes of motion were obtained, which allowed a detailed characterization of the distribution of relaxation times of the complex relaxations observed in indomethacin.

Results. Two different relaxational processes were detected and characterized: the glass transition relaxation, or α-process, and a sub-T_g relaxation, or secondary process. The lower temperature secondary process presents a very low intensity, a very low activation energy, and a very low degree of cooperativity. The fragility index (Angell's scale) of indomethacin obtained from TSDC data is m = 64, which can be compared with other values reported in the literature and obtained from other experimental techniques.

Conclusions. TSDC data indicate that indomethacin is a relatively strong glass former (fragility similar to glycerol but lower than sorbitol, trehalose, and sucrose). The high-resolution power of the TSDC technique is illustrated by the fact that it detected and characterized the secondary relaxation in indomethacin, which was not possible by other techniques.

KEY WORDS: glass transition relaxation, secondary relaxations, glassy state, amorphous state.

INTRODUCTION

It is well known that the dissolution rate and therapeutic activity of a drug depend on its physical state and, particularly, on its degree of crystallinity. The significance of the amorphous state in pharmaceutical systems has been underlined in recent works (1,2). A disordered amorphous material dissolves faster and has a greater solubility than the corresponding ordered crystalline solid. As a consequence, the amorphous form of a drug often shows an improved therapeutic activity. However, the amorphous state is a non-equilibrium state and, consequently, it is unstable. If the molecular motions that originate this instability are not retarded over a meaningful pharmaceutical timescale, a significant variation in some of the key properties of the drug may occur. In this context, the knowledge of the timescales of molecular motions in amorphous systems, *i.e.,* the knowledge of the relaxation map that characterizes the molecular dynamics in a given material is needed for profiting from the advantages of the amorphous state and is an important requirement for a safe storage and use of amorphous pharmaceutical solids (3). Thermally stimulated depolarization currents (TSDC) is a dielectric technique that is able to probe slow reorientational motions and, consequently, is a very suitable technique to study mobility in solids. However, it is unknown in the community of pharmaceutical scientists. One of the purposes of the present work is to address this community to show how TSDC provides relevant information regarding the different modes of motion present in a given pharmaceutical material. To do so, we chose indomethacin as a model pharmaceutical solid. The fact that the molecular mobility in indomethacin has been studied by several experimental techniques (4–6) allows a comparison between the results provided by the different techniques.

MATERIALS AND METHODS

Indomethacin (1-[4-chlorobenzoyl]-5-methoxy-2-methyl-1-H-indole-3-acetic acid) was a Sigma product (catalogue number I-7378, lot 77H18461), with a melting point at 160°C obtained by DSC, and it was used without further purification. Its calorimetric glass transition temperature is reported to be T_g = 42°C (315.2 K) for a heating rate of 1°C/min (7).

TSDC experiments were carried out with a TSC/RMA 9000 instrument (TherMold Partners, Stamford, CT) covering the temperature range between –170 and +400°C. The quantity of substance required to prepare the sample is typically 100–300 mg. Before the TSDC experiments, the sample was heated up above the melting point and cooled down fast from the melt below the glass transition temperature to produce the glassy state.

Description of a TSDC Experiment

In a TSDC experiment, the sample under study is placed between the electrodes of a parallel plane capacitor and is "excited" by polarizing with a dc electric field at a given temperature [the polarization temperature (T_P)] for a given period of time [the polarization time (t_P)]. This is the first step of a TSDC experiment: the polarization step.

The effect of the electric field in the sample is to orient dipoles within the molecular structure, to create in the sample a given amount of polarization. Naturally, because the molecular mobility increases as the temperature increases, the nature and the amount of the polarization created by the electric field depends on the polarization temperature.

The second step of a TSDC experiment consists in cooling the sample down to a temperature $T_P' = T_P - \Delta T$, in the presence of the electric field, to freeze-in the dipolar orientations, *i.e.,* to retain (at least partially) the polarization cre-

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ated by the electric field at the polarization temperature. We will call this step of a TSDC experiment the freezing-in step.

At the end of this step, with the sample at the temperature T_P', the polarizing electric field is removed. Thus, part of the polarization created by polarizing electric field will disappear, but part of that polarization will be preserved. The sample so obtained is thus a stable electret, *i.e.,* a sample presenting a given amount of permanent orientational polarization. This possibility of producing a sample with permanent polarization arises from the fact that the relaxation time of the molecular motions is, in general, temperature dependent, in such a way that it increases with decreasing temperature. Thus, the retained polarization corresponds to dipolar motions that were activated by the electric field at the polarization temperature and whose characteristic time, the so-called relaxation time, $\tau(T)$, is sufficiently temperature dependent to give rise to a "freezing in" of the polarization. Otherwise stated, the retained polarization contains the contribution of the molecular motions that are relatively fast at T_P but that become slower than the time scale of the experiment at T_P'. The state of the sample at the end of the freezing-in step of the TSDC experiment is thus a non-equilibrium state, where the depolarization is prevented by kinetic reasons.

In the third step of a TSDC experiment, the polarized sample is subjected to a constant rate heating process. As the temperature rises, the relaxation time of the molecular motions decreases. The thermal energy flows into the sample, stimulating molecular motions, allowing the return of the sample to the equilibrium state. This is the depolarization step of a TSDC experiment, which is a thermally stimulated recovery process. The depolarization process, which takes place during the constant rate heating ramp, is the adjustment of the polarization as the temperature increases, and it gives rise to a small intensity electric current (I), the depolarization current. This current is measured as a function of temperature and constitutes the experimental output of a TSDC experiment.

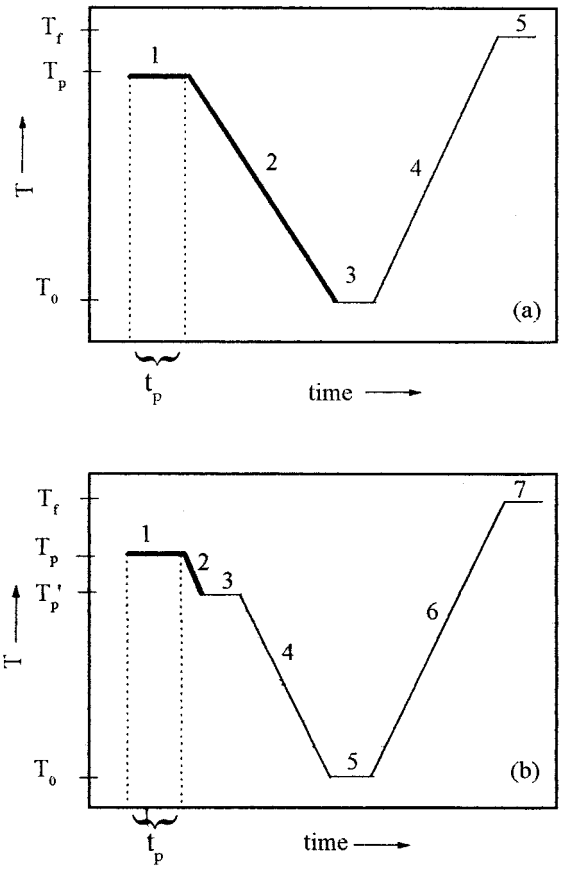

Fig. 1. Schematic representation of a TSDC global experiment (a) and of a thermal sampling (TS) experiment (b). The electric field is on in steps 1 and 2 (thicker lines). The depolarization current is measured during the constant rate heating process [step 4 in (a) and step 6 in (b)]. The width of the polarizing window in a TS experiment (b), $\Delta T = T_P - T_P'$, is typically between 0 and 4°C.

Global Experiments and Thermal Sampling Experiments

Two thermal treatments are most frequently used in TSDC experiments and are shown schematically in Fig. 1.

In Fig. 1a $T_P' = T_0$, *i.e.,* the sample is cooled in the presence of the polarizing field, down to the initial temperature of the linear heating ramp (the freezing temperature). If the temperature interval $\Delta T = T_P - T_0$ is wide, the polarization created in the sample will correspond to a wide variety of dipole motions or to a wide spectrum of relaxations. These TSDC experiments, which are called global experiments, are often used to detect a range of molecular motions or relaxations that are present in a given material. The result of such an experiment is a complex thermogram like those that will be shown later in this work (Fig. 2).

Figure 1b shows a different type of TSDC experiment, which is currently called thermal sampling (TS) experiment (or fractional polarization experiment). In a TS experiment the sample is polarized at T_P during a given time interval, the so-called polarization time (step 1) and is cooled in the presence of the field down to T_P' (step 2). In step 3, the field is removed and the temperature is held at T_P' for a specified period of time. During this period, a partial depolarization takes place. With the field off, the sample is cooled in the absence of the field, down to the freezing temperature (T_0). The objective of the thermal sampling experiment is to freeze a narrow distribution of relaxations or, ideally, to isolate a single, individual dipolar motion. To achieve this objective, the experimental parameters have to be carefully chosen. In this context, the most important parameters are the temperature interval, $\Delta T = T_P - T_P'$, where the electric field acts on the sample, the intensity of the polarizing field (E_P), and the polarization time (t_P). To isolate a single, individual dipolar motion using the thermal sampling procedure, it is advisable to use narrow temperature windows (ΔT), low intensity fields and short polarization times. Increasing the holding time in step 3 of Fig. 1b, the depolarization time t_D, also contributes to narrow the distribution of the polarized modes. It is to be underlined that the modifications of the experimental parameters that lead to a narrowing of the distribution of the polarized modes also lead, at the same time, to a decreasing of the intensity of the TS peak.

The best experimental parameters are to be chosen as a compromise between the width of the distribution and the intensity of the TS signal. Typical values of these parameters often used in TS experiments are $\Delta T = 1 - 3$°C, $E_P = 100$–300 V/mm, $t_P = 0$–5 min, and $t_D = 0$–1 min. Using these parameters with this order of magnitude often allows the fro-

zen-in polarization to approximately correspond to a single, individual dipolar motion. This is indeed a very important feature of the TSDC technique, because the TS procedure (Fig. 1b) allows the polarization of specific segments of a complex global relaxation or, otherwise stated, it permits the experimental deconvolution of a global, heterogeneous relaxation process into its individual, component relaxation modes. Performing different TS experiments in the global peak's temperature region allows the selective activation of the different components of the global peak, *i.e.,* the separation of a broad distribution of relaxations into its narrowly distributed components. Results of different TS experiments will be shown later in this work (Figs. 3, 4, and 9).

A TS peak thus corresponds to the polarization of a narrow distribution of modes of motion or, in the limit, to the polarization of a single mode of motion. Considering a single mode of motion, it is reasonable to assume that, at each temperature of the depolarizing heating ramp, the depolarization process is a first order rate process, *i.e.,* follows a Debye-like decay:

$$J(T) = -\frac{dP(T)}{dt} = \frac{P(T)}{\tau(T)} \tag{1}$$

where $J(T)$ is the depolarization current density at temperature T in the heating ramp, $P(T)$ is the polarization stored by the sample at that temperature, and $\tau(T)$ is the temperature-dependent relaxation time of the mode of motion under consideration. With Eq. (1) it is possible to determine the temperature-dependent relaxation time of each TS peak (*i.e.,* of each relaxation mode) given that $J(T)$ is the output of a TS experiment, and $P(T)$ can be obtained from the area of the TS peak above the temperature T:

$$P(T) = \frac{1}{r}\int_T^{\infty} J(T')dT' = \frac{1}{r}\int_T^{T_f} J(T')dT' \tag{2}$$

where T_f is a temperature well above the temperature of the maximum of the TS peak, where the sample is already completely depolarized. The temperature-dependent relaxation time associated with a given mode of motion can thus be calculated from:

$$\tau(T) = \frac{\frac{1}{r}\int_T^{T_f} J(T')dT'}{J(T)} \tag{3}$$

where $J(T)$ is the depolarization current density measured in the heating ramp of the TS experiment (step 6 in Fig. 1b). This capability of directly calculating the relaxation time from the results of a single TS experiment constitutes a basic quantitative feature of the TSDC technique. Neither dielectric relaxation spectroscopy nor temperature modulated differential scanning calorimetry (TMDSC) are able to determine the temperature-dependent relaxation time of a single (or narrowly distributed) relaxation mode. Instead, the result of the analysis of the data provided by both these techniques is a mean relaxation time of the whole distribution.

The procedure to calculate the log $\tau(T)$ vs. 1/T line for a given TS peak is very common for TSDC users. Readers who are not familiar with this technique should look at references where this problem is described in some detail (8,9). Additional detail concerning the physical foundations of the TSDC technique, and of the nature of the information it provides, can be found in several publications (9–12).

RESULTS AND DISCUSSION

The results of three TSDC global experiments (experimental procedure described in Fig. 1a) that are shown in Fig. 2 indicate that we have at least two relaxations in indomethacin.

One relaxation appears in Fig. 2 at temperatures higher than –25°C, the other appears below –80°C. It is to be noted that –165°C is the lower limit of the temperature range available to our equipment, so that the lower temperature relaxation probably extends down to temperatures below this limit. In the following we report the results of a detailed TSDC study of the different relaxations in indomethacin.

Glass Transition Relaxation

The global peak associated with the higher temperature dipolar relaxation of indomethacin has a maximum intensity at 40°C (see dashed peak in Fig. 3). Given that the calorimetric glass transition temperature is reported to be T_g = 42°C (heating rate of 1°C/min) (7), the observed TSDC peak corresponds to the relaxations that are frozen in at T_g in a DSC experiment. The technique of thermal sampling (TS) was used to analyze the detail of this relaxation. Figures 3 and 4 show the results of some of the TS experiments we carried out on the glass transition relaxation of indomethacin. Figure 3 shows the higher temperature components of the global peak (higher polarization temperatures), whereas Fig. 4 shows TS peaks obtained with lower polarization temperatures.

It should be noted that some TS peaks in Fig. 4 present a kind of bimodal shape that can be ascribed to an overlap between two different relaxations or to a crossover between two different dynamic regimens. This problem will be discussed later.

The lines of $\log_{10} \tau(T)$ as a function of $1/T$, for some of the TS peaks shown in Fig. 3, are presented in Fig. 5.

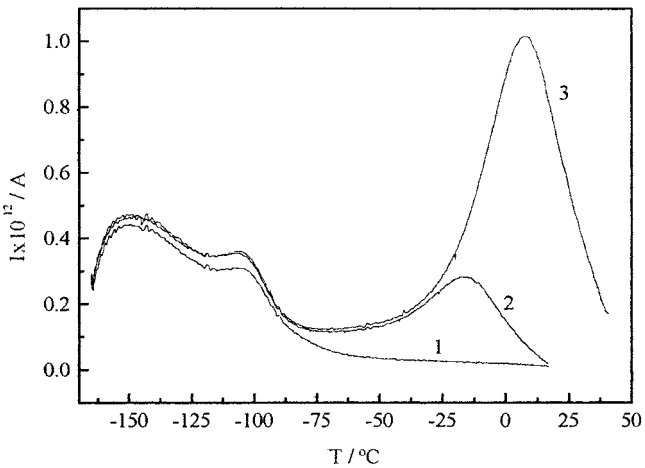

Fig. 2. TSDC thermograms obtained from three global experiments with polarization temperatures, T_P = –80°C (curve 1); –20°C (curve 2), and 0°C (curve 3). The other relevant experimental parameters are strength of the polarizing electric field, E = 300 V/mm, polarization time, t_P = 5 min, freezing temperature, T_0 = -165°C, heating rate, r = 4°C/min.

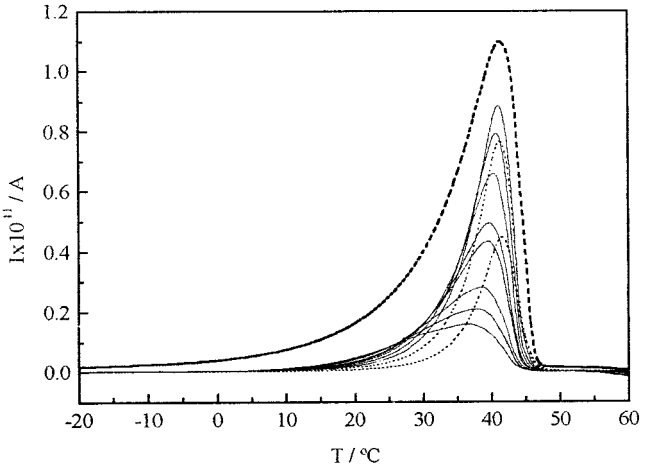

Fig. 3. Higher temperature TS components of the relaxation at ~40°C of indomethacin. The polarization temperatures (T_P) varied between 21 and 39°C, with intervals of 2°C. The strength of the polarizing electric field was E = 200 V/mm, the polarization time was t_P = 3 min, the width of the polarization window was 1°C, and the heating rate was 4°C/min. The dotted peaks, which show decreasing intensity, indicate the border of the transformation to the supercooled equilibrium state. The dashed peak (arbitrary intensity) is a global TSDC peak obtained with a polarization temperature T_P = 45°C, and a freezing temperature T_0 = –20°C (the other experimental conditions are similar to those reported before for the TS experiments).

The observation of Fig. 5 elicits the following comments:

1. The $\log_{10} \tau(T)$ vs. $1/T$ lines of the TS peaks with lower polarization temperature are linear, *i.e.,* show an Arrhenius behavior.

2. The $\log_{10} \tau(T)$ vs. $1/T$ lines of the TS peaks with polarization temperature closer to the glass transition temperature show a significant curvature.

3. The mean slope of these lines increases as the polarization temperature increases.

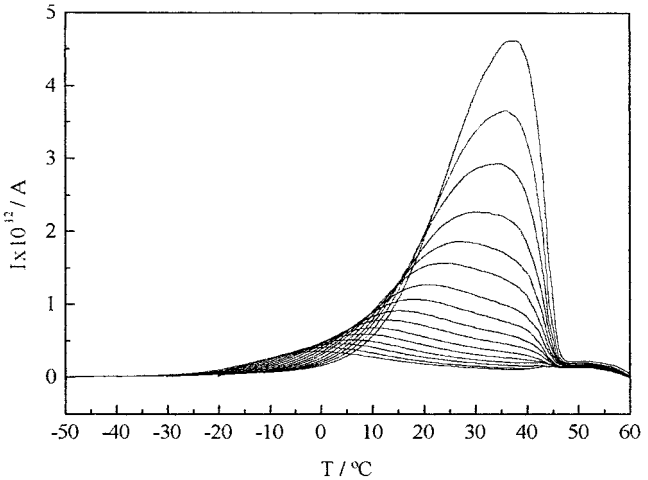

Fig. 4. Lower temperature TS components of the relaxation at 40°C of indomethacin. The polarization temperatures varied between –10 and 20°C, with intervals of 2°C. The strength of the polarizing electric field was E = 200 V/mm, the polarization time was 3 min, the width of the polarization window was 1°C, and the heating rate was 4°C/min.

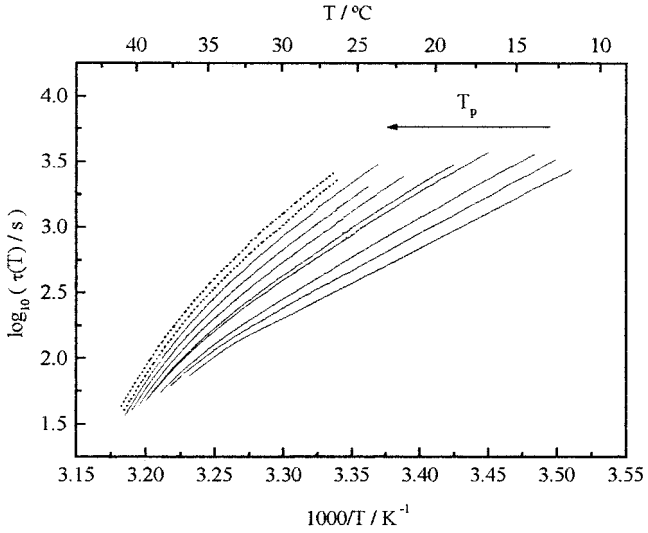

Fig. 5. $\log_{10} \tau(T)$ vs. $1/T$ lines for some TS peaks shown in Fig. 3.

Because the slope of these lines is proportional to the activation energy of the corresponding motional mode, we conclude that the TS peaks with higher polarization temperature correspond to motional processes with higher activation energy.

Note that the depolarization ramp of a TS peak obtained in the glass transition region crosses over from the glassy state where the dynamics shows an Arrhenius behavior to the equilibrium supercooled liquid where the Vogel-Tammann-Fulcher behavior is observed. This transition between the two regimens as one moves from below T_g to above T_g is expected on the basis of both other experimental studies and theoretical considerations. Thus, a TS peak of the glass transition is expected to contain information on the $\tau(T)$ crossover region between the Arrhenius-like behavior of the glassy state and the Vogel-Tammann-Fulcher behavior of the metastable equilibrium supercooled liquid.

When the polarization temperature is far below T_g, the TS peak corresponds to the polarization of a single motional mode, which shows Arrhenius behavior, *i.e.,* a linear $\log_{10} \tau(T)$ v.s $1/T$ line. As the polarization temperature increases and approaches T_g, it enters the temperature region of the crossover. In the case of a fragile system, where the potential energy surface is characterized by a high roughness, the electric field is able, at those temperatures near T_g, to polarize a wide diversity of modes of motion. That is why the $\log_{10} \tau$ vs. $1/T$ lines of the TS peaks in the glass transition region of fragile systems often show a significant curvature. As the depolarization proceeds in the linear heating ramp, the polarized modes depolarize in the order of increasing activation energy (note in Fig. 5 that the slope of the lines increases with increasing temperature).

The $\log_{10} \tau(T)$ vs. $1/T$ lines contain the relevant kinetic information about the polarized motional modes. If they are linear, fitting with the Arrhenius equation allows the determination of the prefactor and of the activation energy, whereas the fitting with the Eyring equation allows the determination of the activation entropy and of the activation enthalpy. For curved $\log_{10} \tau(T)$ vs. $1/T$ lines the kinetic parameters can be obtained at each temperature by using a nonlinear fitting. It is usual to associate to each TS peak a pair of kinetic parameters (activation energy and pre-exponential

factor, or activation enthalpy and activation entropy) calculated at T_m, *i.e.,* at the temperature of the maximum of the current intensity (9,11). Figure 6 shows the activation enthalpy of the TS peaks shown in Figs. 3 and 4 as a function of the temperature location (T_m) of the peaks. The dotted line in Fig. 6 corresponds to the so-called zero entropy approximation and represents the activation enthalpy of the TS peaks that correspond to motional processes with no activation entropy, *i.e.,* to noncooperative modes of motion (10,13).

From Fig. 6 we see that the lower temperature TS peaks of the glass transition relaxation (TS peaks in Fig. 4) have low activation enthalpies and nearly obey the zero entropy approximation. On the other hand, as noted before, these TS peaks have nearly linear $\log_{10} \tau(T)$ vs. $1/T$ lines. Conversely, the higher temperature TS peaks (Fig. 3) show a strong departure from the zero entropy line, such that the amplitude of this departure increases as the polarization temperature increases. Moreover the $\log_{10} \tau(T)$ vs. $1/T$ lines of these TS peaks show a curvature that increases as the polarization temperature increases. Two broad categories of molecular motions are often found in solid materials: (i) local modes and (ii) long-range collective or cooperative modes. The local modes originate from noncooperative motional processes, involving in general small groups of atoms or consisting of small amplitude molecular librations. An elementary, local, noncooperative motional process is such that the interactions between the moving entity and the neighboring atoms and/or molecules are weak. The local motions occur without disturbing the neighbors, so that the activation entropy associated to such a motional process is negligible. The departure from the zero entropy line thus appears as relevant information provided by TSDC regarding the degree of cooperativity of the molecular motions.

It was underlined that some of the peaks shown in Fig. 4 present some bimodal character (*i.e.,* those with polarization temperature between 6 and 14°C), which can probably be ascribed to the overlap of two distinct relaxations. In fact, it seems that we are in the presence of two kinds of TS peaks, as is clearly illustrated in Fig. 7, where the temperature of maximum intensity of the TS peaks (T_m) is plotted against the respective polarization temperature (T_P) for all the peaks shown in Figs. 3 and 4.

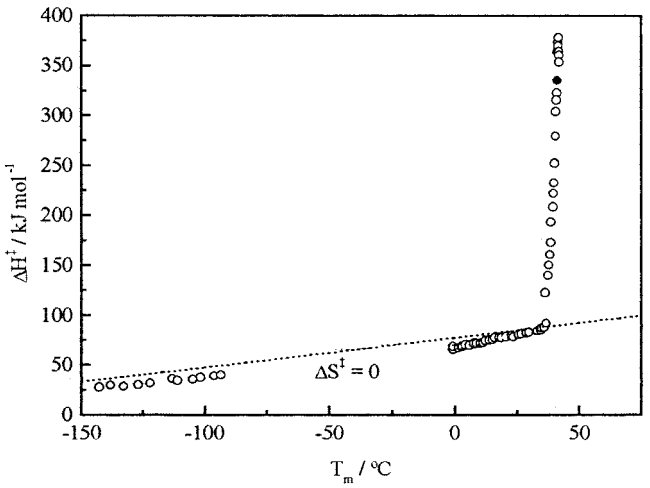

Fig. 6. Activation enthalpy of the TS components of the secondary relaxation and of the α-relaxation of indomethacin as a function of the peak's location (T_m). The continuous line corresponds to the zero entropy prediction. The full symbol corresponds to the TS peak with higher intensity in the glass transition region.

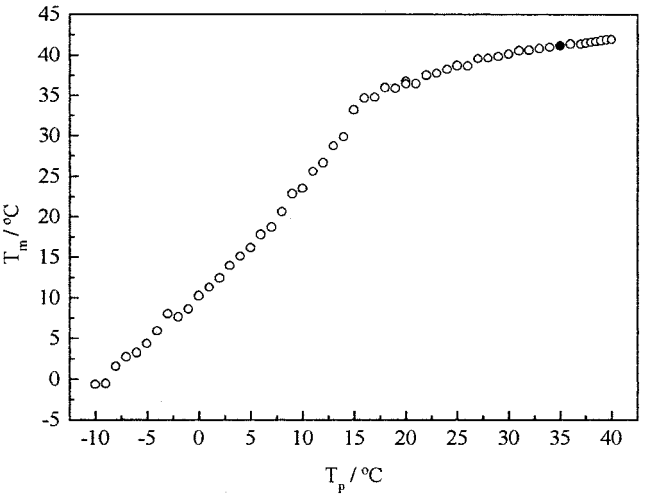

Fig. 7. Temperature of maximum intensity of the TS peaks (T_m) plotted against the respective polarization temperature (T_P) for all the peaks of the relaxation at ~40°C of indomethacin (Figs. 3 and 4).

Figure 7 clearly shows two different regimens: one at higher temperatures ($T_P > \approx 15$°C), roughly corresponding to the TS peaks shown in Fig. 3, where the position of the peaks (T_m) changes very slightly as the polarization temperature increases, and the other at lower temperatures corresponding to the TS peaks shown in Fig. 4, where the peak position shifts continuously to higher temperature as the polarization temperature increases. Besides, as shown in Fig. 6 and discussed before, the higher temperature TS peaks present a strong departure from the zero entropy behavior, whereas the lower temperature TS components correspond to motional processes with negligible activation entropy.

These observations could be compatible with the interpretation that there is, in indomethacin, a secondary relaxation process that is partially disguised by the main α-process. However, the reported behavior just below T_g, *i.e.,* the existence of two distinguishable regions that are separated by TS peaks with some kind of bimodal shape, was observed in other glass formers, polymeric as well as low molecular weighted (namely salol and *m*-toluidine). The reported observations can be interpreted on the basis that, at temperatures 20 or 30°C below the glass transition temperature, there exists a molecular mobility characterized by low-activation energies and a low degree of cooperativity, which is a predecessor (on heating) of the cooperative motions associated with the glass transition relaxation. In the case of indomethacin, this precursor mobility appears in the TSDC spectrum in the temperature region between 0 and 30°C (TS peaks with polarization temperatures between –10 and 15°C), and the corresponding components nearly obey the zero entropy approximation and show activation enthalpies that vary in the range between 66 and 85 kJ/mol.

Glass Transition Temperature Provided by TSDC

Each TS peak in the glass transition region has an intensity and a shape that arise from a compromise between the polarizing efficiency of the electric field (which increases as

the molecular mobility increases, *i.e.,* as the polarization temperature (T_P) increases) and the tendency of the polarization to disappear during the no-field cooling step (which is particularly effective near and above T_g). For polarization temperatures far below T_g, only the lower activation energy modes had enough time to be activated (small and broad TS peaks in Fig. 4). As the polarization temperature approaches T_g, the electric field is allowed (in the same polarization time (t_P) equal for all experiments in Figs. 3 and 4) to activate barriers with increasing amplitude (the TS peaks show higher intensity and steepness in Fig. 3). When the polarization temperature (T_P) exceeds a given temperature in the vicinity of T_g, a large part of the modes are depolarized during the no-field cooling, *i.e.,* in steps 3 and 4 of Fig. 1b (dotted TS peaks in Fig. 3, showing a decrease of intensity).

The TS peaks in the glass transition region with maximum intensity at $T_m < T_M$ thus correspond to lower activation energy modes, whereas the TS peaks with maximum intensity at $T_m > T_M$ show decreasing intensities because the freezing-in of the polarization becomes increasingly difficult as the temperature increases, indicating the rapid recovery to the equilibrium state of the non-equilibrium glass. The TS peak with the single largest maximum intensity in the glass transition region, which is located at T_M, is the peak where a higher extent of polarization was allowed to be "frozen-in," and it corresponds to a situation in which the electric field was allowed to polarize nearly all the higher activation energy motional modes associated with the glass transition relaxation. Above T_M the depolarization becomes very fast, preventing the retention of the polarization. That is why the intensity of the maximum of the TS peaks above T_M in the glass transition region decreases sharply as T_P increases (dotted peaks in Fig. 3). This is also the reason why the TS peaks in the glass transition region present a shape such that there is a sharp decrease of the current intensity (a fast depolarization) above the temperature of maximum intensity. Above T_M the "freezing-in" of the polarization is increasingly difficult, indicating the transformation to the equilibrium (ergodic) metastable supercooled liquid state.

The temperature T_M of the TS peak with maximum intensity in the glass transition region thus represents the lower limit (the onset) of the transition range between the non-equilibrium glass and the phase into which it transforms by heating (metastable supercooled liquid, orientationally disordered crystal, liquid crystal, *etc*). Thus, it can be considered as the glass transition temperature provided by the TSDC technique at the heating rate of the experiment.[1] The relaxation time at this temperature, $\tau(T_M)$, is in the lower limit of the times probed by the TSDC technique. In fact, the relaxation time at T_M calculated from TSDC data is of the order of 10–30 s, and this is observed for polymeric materials, as well as for molecular glasses and orientational glasses. The glass transition temperature provided by the TSDC technique (T_M) thus corresponds to the temperature at which the relaxation time decreases to 10–30 s on heating from the glassy state. Thus, it defines a timescale of the system when nearly all activation barriers are activated, *i.e.,* a time-scale of the system very near the equilibrium.

[1] Note that T_M is not only dependent on the heating rate. The thermal treatments that the sample underwent before the application of the polarizing field, *i.e.,* the cooling rate used to prepare the glass from the melt, can also influence the value of T_M.

Fragility Index of Indomethacin

The glass transition temperature provided by the TSDC technique (T_M) is thus a characteristic temperature defining the crossing of the timescale of the heating rate of the TS experiment with the timescale of the equilibrated glass. In this context, the choice of T_M appears as a reference temperature defining an identical timescale on heating for all samples (if the heating rate is the same) and an identical polarization condition. That is the reason why T_M was chosen as a reference temperature to determine the fragility of a glass former from TSDC data.

In fact, if we consider the TS peak with highest intensity in the glass transition region (located at T_M), the TSDC fragility index, m_1, was defined as (9,10)

$$m_1 = \left(\frac{d \log_{10} \tau(T)}{d(T_M/T)} \right)_{T=T_M} \tag{4}$$

or, alternatively,

$$m_1 = \frac{1}{2.303} \left[1 + \frac{\Delta H^{\neq}(T_M)}{RT_M} \right] \tag{5}$$

where $\Delta H^{\neq}(T_M)$ is the activation enthalpy at T_M of the higher intensity TS component of the glass transition peak. The temperature of maximum intensity of the TS peak in the glass transition region of indomethacin is T_M = 42.05°C = 315.2 K, and the activation enthalpy at T_M is $\Delta H^{\neq}(T_M)$ = 383 kJ/mol, so that the TSDC fragility of indomethacin is m_1 = 64. This value is to be compared with the values of m = 76.7, obtained from the heating rate dependence of the calorimetric glass transition temperature (5), and m = 67, obtained from dielectric relaxation data in the frequency range from 10 to 10^5 Hz (5).

Table I shows the TSDC fragility (m_1) for different molecular glass formers, as well as the fragility values reported in the literature and obtained by other experimental techniques.

On the other hand, Fig. 8 shows an Angell-type plot of $\log_{10} [\tau(T)/\tau(T_M)]$ vs T_M/T for the TS peak of maximum intensity of the different glass forming materials presented in Table I. In this representation $\tau(T_M)$ is the relaxation time at the temperature of the maximum of the TS peak. The dashed line is the representation of $\log_{10} [\tau(T)/\tau(T_M)$ vs. T_M/T line for the zero entropy prediction, which represents the limit of behavior for infinitely strong glasses. The fragility m_1 of a

Table I. Glass Transition Temperature (T_g) and Fragility Index of Some Molecular Glass Formers[a]

Glass former	T_g (K)	m	m_1
Cyano-adamantane	177	35 (14)	20.5 (15)
Glycerol	185	53 (14)	58 (9)
m-Toluidine	187	79 (16)	83 (11)
Salol	220	73 (14)	65 (9)
Sorbitol	272	93 (14)	74 (17)
Maltitol	311	80 (18); 75 (19)	74 (9)
Indomethacin	315	77 (5); 67 (5)	64

[a] The values m are taken from the literature, while m_1 is calculated from equation (5).

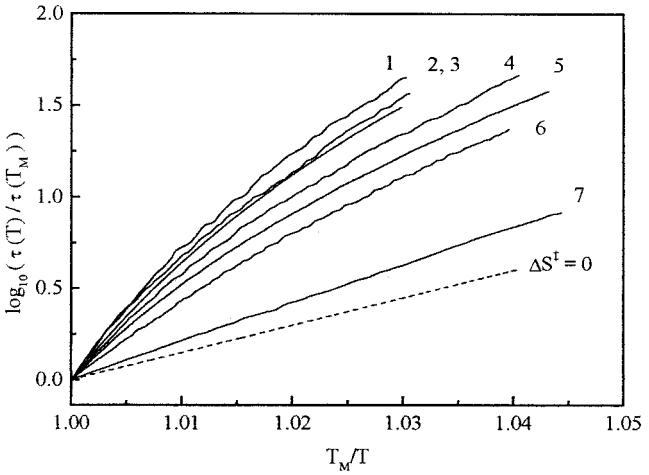

Fig. 8. Angell-type plot of $\log_{10}[\tau(T)/\tau(T_M)]$ vs. T_M/T for the TS peak of maximum intensity of the different glass forming materials. 1, *m*-toluidine; 2, maltitol; 3, sorbitol; 4, salol; 5, indomethacin; 6, glycerol; and 7, cyanoadamantane. The dashed line corresponds to the zero entropy behavior (infinitely strong glasses).

given glass former corresponds to the difference between the slope at $T = T_M$ of the corresponding line in Fig. 8 and the slope of the line for the zero entropy prediction (dashed line). The different curves in Fig. 8 are numbered in the order of decreasing fragility. In this figure, *m*-toluidine is the most fragile liquid (curve 1), whereas cyanoadamantane is the strongest liquid (curve 7). It can be seen that curve 5, which corresponds to indomethacin, is situated between curve 6 of glycerol and curve 4 of salol.

Secondary Relaxation in Indomethacin

In the lower temperature limit of our TSDC equipment, between –165 and –80°C, a secondary relaxation was detected (see Fig. 2). Figure 9 shows some TS components of this relaxation. These components have kinetic parameters such that the zero entropy behavior is followed, as shown in the lower temperature side of Fig. 6. The very low intensity of this relaxation, together with the reported zero entropy behavior and low activation enthalpy (between 28 and 40 kJ/mol, as shown in Fig. 9), indicate that it corresponds to very localized and low amplitude molecular motions. Note that this secondary process in indomethacin was not observed by other techniques and is not reported until now in the literature.

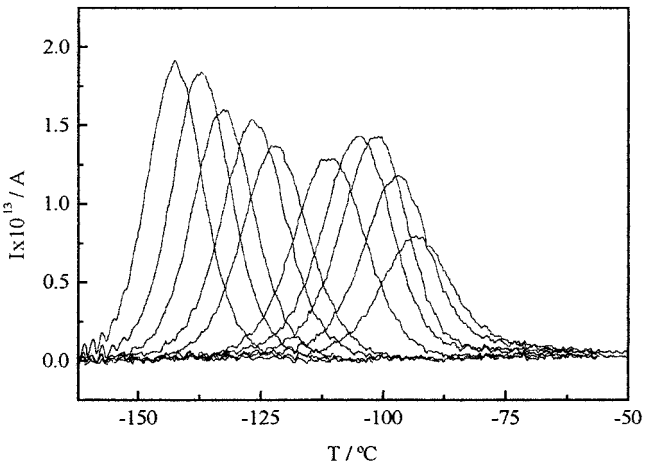

Fig. 9. TS components of the lower temperature relaxation of indomethacin. The polarization temperatures were the following: T_P = –145; –140; –135; –130; –125; –115; –110; –105; –100; –95°C. The strength of the polarizing electric field was E = 400 V/mm, the polarization time was 5 min, the width of the polarization window was 2°C, and the heating rate was 4°C/min.

CONCLUSIONS

From the TSDC analysis of indomethacin reported before, we can draw the following conclusions:

1. The highest intensity component of the glass transition relaxation has a temperature of maximum intensity at T_M = 42.0°C for a heating rate of 4°C/min. This is the glass transition temperature, for that heating rate, provided by the TSDC technique, and it agrees very well with the calorimetric glass transition temperature, which has been reported to be T_g = 42°C (315.2 K) for a heating rate of 1°C/min.
2. On the basis of the TSDC data, indomethacin appears as a relatively strong glass former, with a fragility index in the Angell scale of m = 64 (fragility comprised between those of to glycerol and salol, but lower than sorbitol, trehalose, and sucrose).
3. TSDC data strongly suggest that indomethacin shows a secondary relaxation, with very low intensity and appearing at low temperatures. The corresponding motions have very low activation energy (between 28 and 40 kJ/mol) and probably correspond to very localized and low amplitude molecular motions.

It is indubitable, from the present work, that the TSDC technique appears as a powerful tool to detect and quantitatively characterize the motional processes present in indomethacin. The displacement current that is measured in a TSDC experiment is a direct manifestation of the dipolar motions, *i.e.,* of the molecular mobility. The thermal sampling procedure allows a detailed study of the complex motional processes, *i.e.,* the separation of a complex distributed relaxation into its individual, nondistributed components. Moreover, the TSDC technique allows one to directly calculate the temperature-dependent relaxation time, $\tau(T)$, from experimental data. In this context, from the temperature dependence of the relaxation time, it provides very precise information on the kinetic parameters of these individual components, on the degree of cooperativity of the molecular motions, and on the nature of the distribution of the relaxation times. Finally, TSDC provides a straightforward method for the determination of the fragility index of a glass former. The value obtained for indomethacin shows that it is a molecular glass former stronger than most carbohydrates and with a fragility between those of glycerol and salol.

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