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Research paper

Polymorphism of Irganox 1076®: Discovery of new forms and direct characterization of the polymorphs on a medical device by Raman microspectroscopy

Johanna Saunier [a,*], Vincent Mazel [a], Céline Paris [b], Najet Yagoubi [a]

[a] Laboratoire "Matériaux et santé", IFR 141, UFR de pharmacie, Université Paris-Sud 11, Châtenay Malabry, France
[b] LADIR-UMR 7075 CNRS & Université P. et M. Curie, Thiais, France

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ABSTRACT

Irganox 1076® (octadecyl-3,5-di-tert-butyl-4-hydroxyhydrocinnamate) is a common phenolic antioxidant used in many polymer-based medical devices. As with many organic compounds, several polymorphs exist. However, in literature, only two forms of Irganox 1076® have been mentioned. In this study, we were able to produce, by crystallization in different solvents, three distinct polymorphs, which were characterized by DSC, FTIR and PXRD. Moreover, the three polymorphs have long-time stability at ambient pressure and temperature, meaning that they can potentially be present in or on polymeric devices. During DSC measurements, a fourth polymorph, which was only stable at low temperature, was evidenced.

Thanks to Raman microspectroscopy, Irganox 1076® was identified directly on commercial polyurethane catheters which exhibited a blooming phenomenon. This study proves that the polymorph identified on the surface is different from the commercially available Irganox 1076®. These results emphasize the importance of the screening of polymorphs before any study of the biocompatibility of antioxidants used in medical devices.

1. Introduction

Polymorphism is the ability of a crystalline material to exist in more than one crystal structure and many molecules are concerned by this phenomenon. Due to the different structures, polymorphs may have different melting points, dissolution rates, optical properties or solid state reactivity. As a consequence, polymorphism may have dramatic effects; for example, the bioavailability of a drug in the body will be affected by its polymorphism. In the pharmaceutical field, the presence or the growth of a new polymorph can thus be catastrophic, as happened with the HIV protease inhibitor ritonavir [1].

Formation of a polymorph depends on its stability, and on the condition of the crystallization process [2] (the effect of the solvent, the presence of impurities, the level of supersaturation, temperature, etc.). The search for polymorphs is a complex and empirical task in which both thermodynamic and kinetic effects play an important role. To study the thermodynamic stability relationships of polymorphs, the thermodynamic rules established by Burger and Ramberger [3,4] (heat of transition, heat of fusion and density rules) and free energy change-temperature diagrams are generally used.

A great number of organic compounds are concerned by polymorphism. On more than 150 compounds studied, Kuhnert-Breandstätter et al. [5–12] showed that more than 30% do indeed have polymorphs. In this paper, we focus on the polymorphism of octadecyl-3,5-di-tert-butyl-4-hydroxyhydrocinnamate, usually known as Irganox 1076®, a phenolic antioxidant commonly used in polymers for medical devices (Fig. 1), which figures on the list of plastic additives published in the European Pharmacopoeia.

Antioxidants are usually highly soluble in the polymer at elevated processing temperatures, but on cooling, the polymer may become supersaturated with the stabilizer. This can result in a surface segregation and a crystallization process of the additive [13,14] in one of its polymorphic forms on the surface of the polymer. As the study of extractable and leachable compounds is a key point for medical devices that are invasive and implanted into the human body, identifying the nature of the polymorphs on the catheter is an important task: the leachability might be thus modified depending on the polymorph (different dissolution rates and solubility), and the surface properties that condition biocompatibility and bioadhesion may also be affected by the nature of the polymorph (surface energy, crystal morphology) [16,17,19,25,26].

* Corresponding author. Laboratoire "Matériaux et santé", EA 401, IFR 141, UFR de pharmacie, Université Paris-Sud 11, 92296 Châtenay Malabry, France. Tel.: +33 1 46 83 59 50; fax: +33 1 46 83 59 63.
E-mail address: johanna.saunier@u-psud.fr (J. Saunier).

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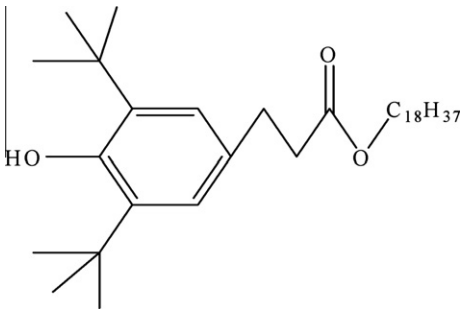

Fig. 1. Formula of Irganox 1076®.

Few publications have been dedicated to the polymorphism of polymer additives, but several phenolic antioxidants are known to have polymorphs, for example, 9-bis-2,4,8,10-tetraoxaspiro-[5,5]-undecane (AO 80) [15], *N,N′*-1,6-hexanediylbis[3,5-bis(1,1-dimethylethyl)-4-hydroxybenzenepropanamide (Irganox 1098®) [16], 1,1,3-tris(2-methyl-4-hydroxy-5-tert-butyl-phenyl)-butane (topanol CA®) [17], and 1,2-bis(3,5-ter-butyl-4-hydroxyhydrocinnamoyl)hydrazine [18]. The most widely studied was tetrakis[3(3, 5-di-ter-butyl-4 hydroxyphenyl)propionyloxymethyl] methane (Irganox 1010®) [19–24], for which at least four polymorphs were found.

Little information is available on polymorphism of Irganox 1076®. Molt and Ihlbrock [27] mention the existence of two forms alpha and beta that can be distinguished by near IR spectroscopy. So, in this paper, a more complete study of the polymorphs of this compound is presented. The results were then applied to a commercial catheter made of polyurethane and containing Irganox 1076® as an antioxidant.

2. Materials and methods

2.1. Catheters

The catheters had an external diameter of 4 mm. and were made of Pellethane 2363 80AE® (Dow Chemical), a poly (ether urethane) with aromatic groups. Pellethane® was supplied in the form of catheters by the Vygon Company, Ecouen, France. All catheters were stored at 4 °C.

2.2. Irganox 1076 (Fig. 1)

Irganox 1076® is a sterically hindered phenolic antioxidant and was supplied by Ciba in the form of a fine white powder. The different polymorphs were obtained by dissolving the commercial powder in different solvents (at concentrations around 0.4 g/mL) with a very slight heating (around 40 °C) in a glass crystallizer. Solvents of different polarities were used: toluene, cyclohexane, methylcyclohexane, tetrahydrofuran (THF), ethylacetate, acetonitrile (ACN), acetone and chloroform. All solvents were supplied by Merck (Fontenay-sous-bois, France). The recrystallization temperature was controlled at 35 °C under ambient atmosphere.

2.3. Fourier transform infrared spectroscopy (FTIR)

The spectrometer apparatus was a Perkin Elmer Spectrum 2000 using the Attenuated Total Reflection (ATR) mode with a diamond crystal (Golden Gate – Specac). Each spectrum was taken with an accumulation of eight scans in the range from 4000 to 550 cm^{-1} with a resolution of 4 cm^{-1}. Heating ATR (DuraSampIR II, SensIR Technologies) was used to follow the phase transitions with the temperature.

2.4. Powder X-ray diffraction (PXRD)

Powder X-ray diffraction (PXRD) analyses were performed on a diffractometer using a PANalytical X-ray generator with a copper anode (voltage: 40 kV, current: 40 mA). Diffractograms were acquired between 6° and 30° (2θ angle) with an angular step of 0.02° and an acquisition time of 5 s per step. Angular calibration was performed with silicon reference.

2.5. Raman spectroscopy

Raman spectra were recorded with a Horiba Jobin Yvon HR 800 spectrometer, using the 514 nm wavelength of an air-cooled argon-ion laser. The laser was focused on the samples by a reverse microscope using a 100× objective lens, allowing a spatial resolu-

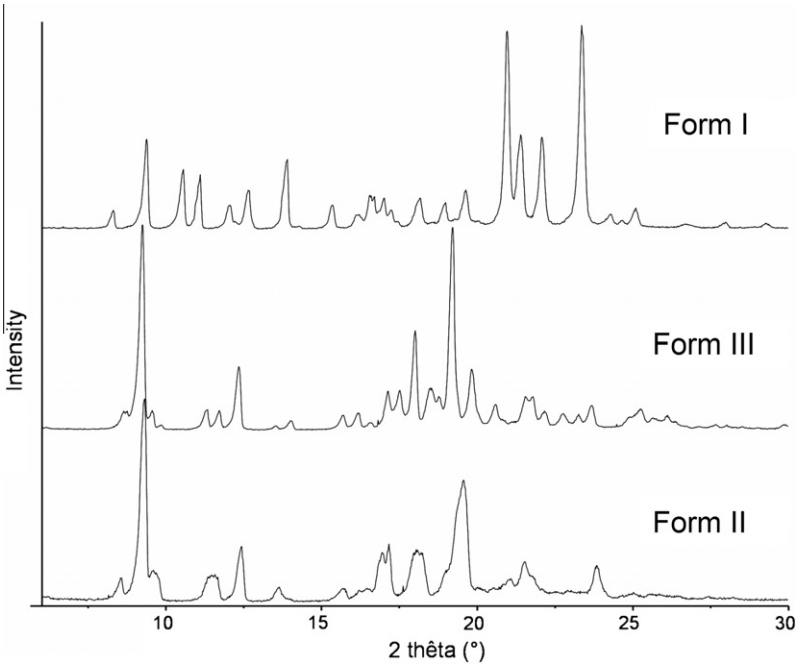

Fig. 2. Diffractogram of the forms I–III.

tion close to 2 μm. The grating had 600 lines/mm, giving a spectral resolution of about 3 cm^{-1} in the 1000 cm^{-1} region. The Raman signal was detected using 25 lines of a 256 × 1024 air-cooled CCD detector. An accumulation time of 600 s was used for each spectrum with a maximum laser power of 200 μW on the sample. Spectra were recorded using two windows between 200 and 1900 cm^{-1} and between 2600 and 4000 cm^{-1}.

2.6. Differential scanning calorimetry (DSC)

DSC scans were performed on a TA Instrument Q1000. The temperature range investigated was between −20 and 80 °C. Aluminum pans were used. The heating rates chosen were 10 °C/min, 0.5 °C/min and 0.1 °C/min. 10 °C/min rate was used to scan a wide range of temperatures (−20 to 80 °C). Experiments were carried out under nitrogen blanketing. Melting enthalpies and melting temperatures were calculated, by carrying out five different analyses at 0.5 °C/min for each sample. The 0.1 °C/min rate was used to increase the resolution in order to evidence the crystallization process during melting. Powder mass was between 1 and 3 mg. Calibration was performed with gallium reference. Films of Irganox were ground before analysis.

2.7. Thermomicroscopy

An Olympus BH-2 (10×) coupled with a heating plate Mettler FP52 and a Sony camera were also used to observe additive melting on the catheter surface.

2.8. Scanning electron microscopy (SEM)

The morphology of catheters was analyzed using a SEM LEO 1530 equipped with a field emission gun GEMINI. Samples were first coated with a silver lacquer and then metallized with a CRESSINGTON 208 HR Sputter Coater.

3. Results and discussion

3.1. Study of the polymorphs of Irganox 1076®

3.1.1. Physico-chemical characterization of different forms

Recrystallization of the commercial powder made it possible to obtain three different polymorphs that will be called forms I–III. Form I is the form commercially available. Forms II and III were

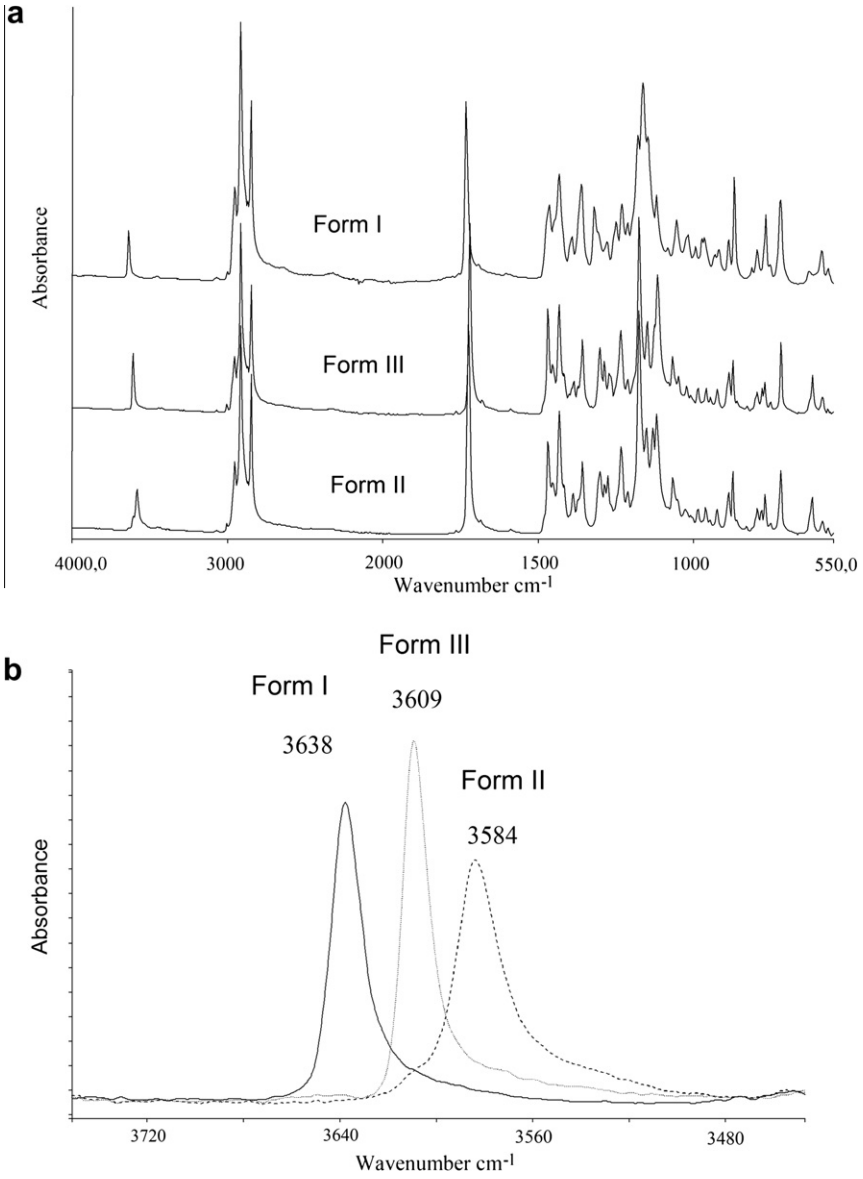

Fig. 3. FTIR ATR spectra (a) of the three forms from 4000 to 550 cm^{-1} (b) of the three forms on the region corresponding to phenol elongation vibration.

obtained by recrystallization in acetonitrile and methylcyclohexane, respectively. In order to name the different forms, we used the convention given by Borka [28] (the high temperature melting form was denoted as form I and then forms II and III in order of their decreasing melting points).

The different forms are easily distinguished by powder X-ray diffraction (Fig. 2). Diffractograms are clearly different as would be expected for different crystallographic forms. Structure determination based on these diffractograms could be performed in a forthcoming study.

FTIR spectroscopy appears as a complementary technique for the differentiation of the three polymorphs. Vibrational spectroscopy is often used in polymorph characterization [1,29–31] since in different crystal structures, interactions between the molecules are not the same. This can lead to variations in the frequency of some vibrations and then to the shift of infrared bands.

Crystallization in solvents can, in some cases, lead to the formation of pseudopolymorphs by cocrystallization with the solvent. In our case, form III cannot be a pseudopolymorph since it can be obtained in different solvents. The case of form II is more questionable as it only crystallizes in acetonitrile. Nevertheless, in this case, the bands corresponding to acetonitrile molecules should appear in the infrared spectra, which is not the case (Fig. 3a). The presence of solvate can definitively be rejected.

However, band shifts can be observed which allow for the differentiating of polymorphs (Fig. 3a). The shift of the phenol band (in the 3550/3650 cm^{-1} region) is a very efficient tool to distinguish the different forms (Fig. 3b). Other characteristic bands are worth noting,

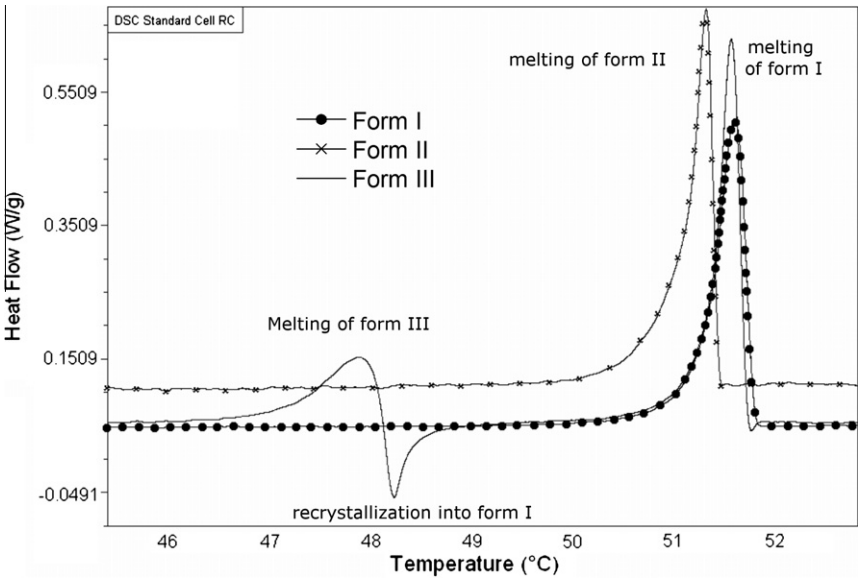

Fig. 4. DSC thermogram of the forms I–III; $V = 0.1$ °C/min.

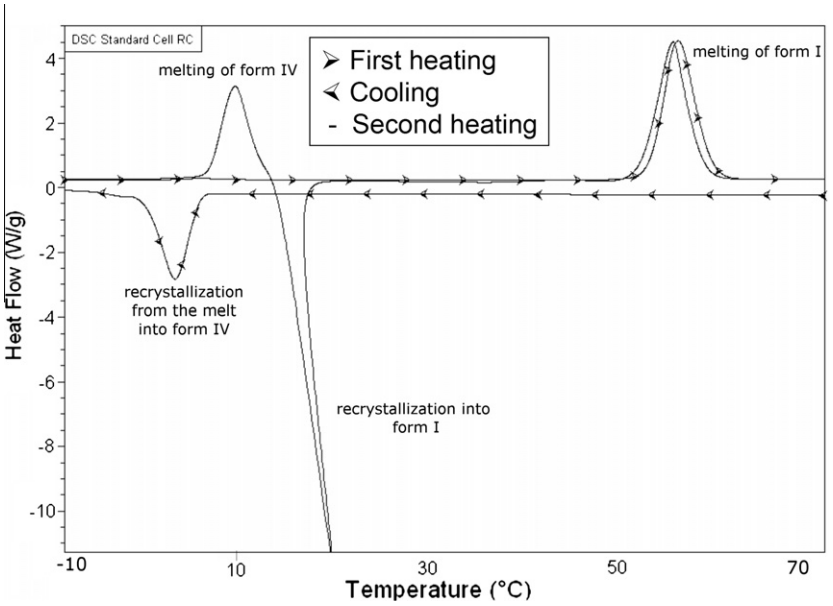

Fig. 5. DSC thermogram of the commercial powder. $V = 10$ °C/min (from −20 to 80 °C but only the thermogram between −10 and 75 °C is shown). A single endotherm corresponding to melting was observed during the first heating. During the cooling, an exothermic peak corresponding to crystallization of Irganox 1076® occurred at 2 °C. During the second heating, three transitions were observed: the melting of the low temperature form, the crystallization in another form followed by the melting of this new form.

such as the C=O stretching band (in the 1720/1740 cm^{-1} region), whose frequency is also sensitive to the nature of the polymorph. These two shifts are probably due to change in hydrogen bonds between the molecules in the different forms. Form I has the FTIR spectra which differs the most with some bands that only exist for this form (for example at 1320, 1165 cm^{-1}) or bands that are only absent for this form (1288 cm^{-1}).

As different crystal structures usually lead to different thermal properties, the three polymorphs were then characterized by DSC.

Thermograms of form III were clearly different from the others (Fig. 4). Moreover, DSC measurements also highlighted the presence of another form. On cooling the melted Irganox, no recrystallization process was indeed observed around 50 °C as could have been expected. The liquid remained in a super-cooled state until the temperature reached approximately 5 °C where an exothermic event was observed. When the sample cooled to −20 °C was reheated, melting was observed at 5 °C, immediately followed by a recrystallization. The new solid melted then at around 50 °C (Fig. 5). This experiment showed that there is another polymorph form that is only stable at low temperature and will be called form IV. Although no polymorphism was mentioned, this phenomenon was also reported by Földes [25]. XRD and FTIR analyses were not performed on this polymorph due to the difficulties of measuring at low temperature.

The melting characteristics of the four forms are the following (n = 5). Form IV melts at 5.3 ± 0.3 °C, form III at 47.2 ± 0.1 °C (T_{peak} = 48.2 ± 0.2 °C), form II at 50.9 ± 0.1 °C (T_{peak} = 51.1 ± 0.1 °C) and form I at 51 ± 0.2 °C (T_{peak} = 51.6 ± 0.1 °C). Melting enthalpies for forms I and II are respectively 116 ± 4 and 115 ± 4 J/g. Melting enthalpies cannot be calculated for forms III and IV because of concomitant crystallization during melting. For form III, recrystallization may be due to the presence of a small amount of form I which allows for the nucleation of this form. Then, the melting of form I was observed at higher temperature.

There is a great similarity between melting temperatures (onset) and enthalpies of forms I and II. As a consequence, a solid/solid transition between form I and II that might occur before melting would be difficult to detect by DSC. To confirm the absence of solid/solid transition between form I and II, FTIR spectroscopy was used. By following the phenol band between 46 and 55 °C thanks to a ATR heating device, only a solid/liquid transition for form II and I was detected. There was no solid/solid transition between form II and I when heating form I and II until melting point (Fig. 6).

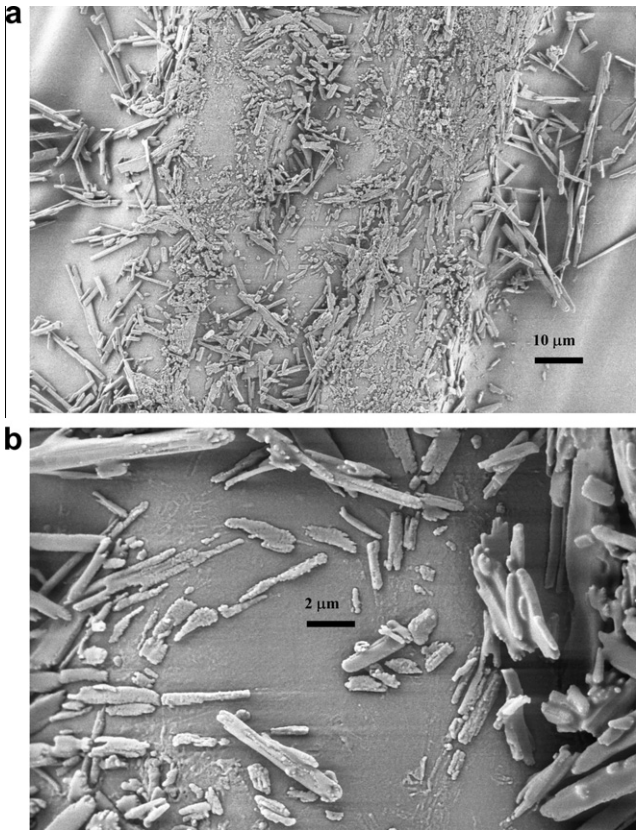

Fig. 7. SEM pictures of the catheter surface covered by needles: (a) G = 1000× and (b) G = 5000×.

3.1.2. Production and stability of the different polymorphs

3.1.2.1. The effect of the solvent. As mentioned above, acetonitrile made it possible to obtain form II and methylcyclohexane form III. Nevertheless, it is difficult to ensure that these forms are perfectly pure.

Other solvents were tested. The use of chloroform, THF and toluene led to the formation of form III. Recrystallization in acetone gave form I. Finally, in ethyl acetate and cyclohexane, blends of the different forms were obtained. However, the choice of solvent

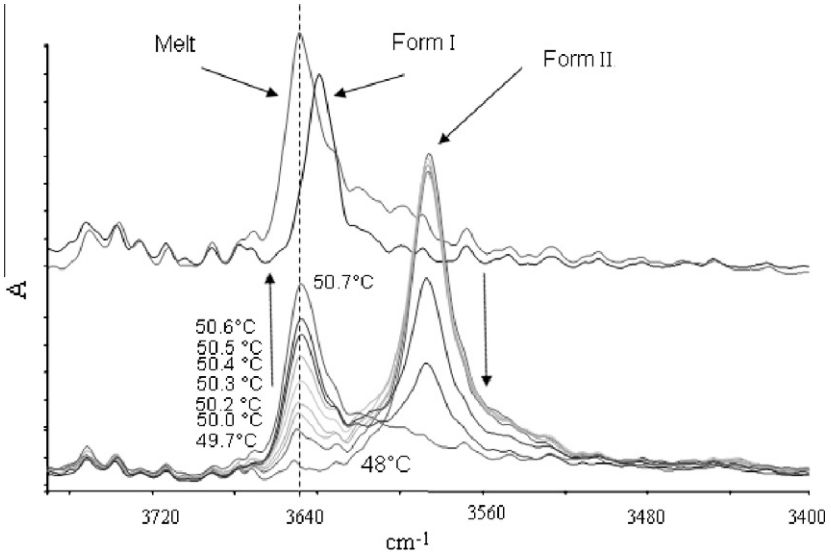

Fig. 6. Evolution of the OH band of form II with temperature (from 48 to 50.7 °C). Spectra of melt Irganox 1076® and form I are given as references. Arrows indicate the evolution of each band when form II was heated.

is not the only important parameter: concentration and temperature of recrystallization are key points. If recrystallization is quite slow, form I is generally the major compound obtained.

3.1.2.2. Stability of the forms. In the DSC measurements presented above, no solid–solid transition that could indicate enantiotropic relations between the polymorphs has been detected, including at very low heating rate (0.1 °C/min). So all the polymorphs seem to be monotropically related. Of course one must bear in mind that a kinetically hindered enantiotropic transition could exist. Comparison of melting temperature and enthalpy between the different forms can also be a means of differentiating monotropic and enantiotropic systems. In an enantiotropic system, the highest melting polymorph will have the lowest heat of fusion and if the highest melting polymorph has the highest heat of fusion, the system is monotropic. In our case, the value of the melting point and enthalpy is so close for forms I and II that it is difficult to conclude. As said above, form IV melts at around 5 °C and immediately recrystallizes into form I (Fig. 4). If we measure the enthalpy of these two events (around 60 J/g for the melting and 80–85 J/g for the recrystallization), even if they are not the true values due to overlap of the two phenomena, we are certain that, at this temperature, enthalpy of recrystallization of form I is greater than the enthalpy of melting of form IV. This proves that forms IV and I are monotropically related, form I being the more stable form. For form III, even at high heating rates, the overlap is too great to conclude. In the hypothesis of monotropic relations, form I is likely to be the most stable form as it is the form with the highest melting point. This is consistent with the fact that the commercial form is form I.

Even if only one stable form at ambient pressure and temperature is expected, it appeared that forms I–III can be kept for a long period under ambient conditions. Spectra taken 110 days after the preparation do indeed not show any evolution.

3.1.2.3. The effect of crystallization conditions of the melted powder. As mentioned above, liquid Irganox 1076® can easily be kept in supercooled state at ambient pressure and temperature for several minutes.

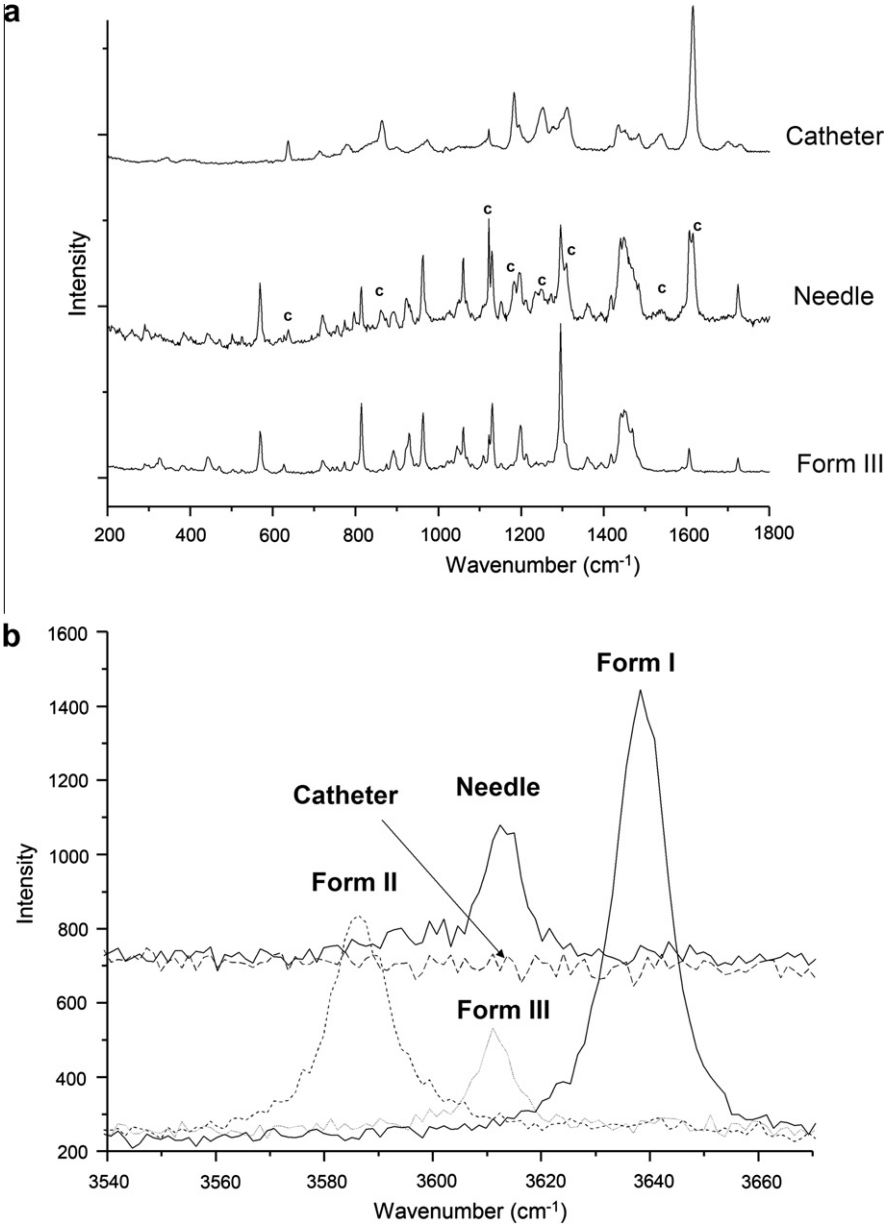

Fig. 8. (a) Raman spectra of the catheter, of a needle and of form III. "c" indicates bands belonging to catheter and (b) Raman spectra of the three forms and of the needle.

Nevertheless, left unattended, it slowly recrystallizes into form I. If some constraint or contact occurs, form III or a blend of forms I and III is obtained.

3.2. The identification of a polymorph on a medical device

3.2.1. Microscopic observations

When the catheter was stored at 4 °C, a blooming phenomenon occurred and white blooms appeared on the surface of the catheter. SEM observation showed that the surface was covered with needles (Fig. 7). The sizes of the needles were generally comprised between 1 and 10 μm length and between 0.5 and 2 μm width.

To identify these needles, thermo microscopy was performed. The surface of the catheter was observed with 10× lens during heating. The clusters on the surface began to melt or disappear as from 46 °C. The melting of all the needles was observed at above 51 °C. These temperatures are coherent with the melting of Irganox 1076® as observed by DSC.

3.2.2. Raman microscopy

In order to identify the product observed on the surface, Raman spectroscopy was used. This technique does have the great advantage of making it possible to focus on small particles, thanks to the use of microscopy, without any sample preparation. During the experiment, a laser was focused onto several needles and onto the polyurethane surface. Forms I–III of Irganox 1076® were also analyzed.

Comparison of the spectra in the region between 200 and 1900 cm^{-1} facilitated identification of the needle as Irganox 1076®. Some additional peaks were found in the spectrum of the needles that can be attributed to the polymer (Fig. 8a). A close comparison of the spectrum showed small differences between the spectra of the polymorphs and made it possible to identify each polymorph. The spectral region of the vibration of OH from the phenol function is the more suitable for identification. Indeed, as during the infrared measurements, the position of the band differed for each of the polymorphs. This band was located at 3586 cm^{-1} for form II, 3638 cm^{-1} for form I and 3610 cm^{-1} for form III. For the needles on the catheter, the band was at 3610 cm^{-1} (Fig. 8b), proving that Irganox 1076® crystallizes at the surface of the catheter into form III. It then differs from the form commercially available.

4. Conclusion

In this study, four different polymorphs of Irganox 1076® were characterized using several analytical techniques. We proved that three of them have long-time stability at ambient pressure and temperature. Thanks to Raman microspectrometry, it has been possible to identify the polymorph present at the surface of a commercial catheter after the blooming effect, as form III. It is thus different from the commercially available form (form I).

This is a very important result for the study of leachable components of the catheter. For this study, blooming was observed at 4 °C, which is not a common storage temperature for medical devices. However, it evidenced that blooming can occur if storage temperature is too low and that some care must be taken for the storage of such devices. The temperature at which blooming occurs depends on the solubility of the additive in the polymer. So, it is influenced by the physico-chemical properties of the additive and the polymer and by the additive concentration. It is important to consider the right polymorph for the study of the leachable compounds, because physical properties such as dissolution rate and solubility could differ from one form to another. Moreover, different surface energies and crystal morphologies may have different impacts on the biocompatibility of the medical device.

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