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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

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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].

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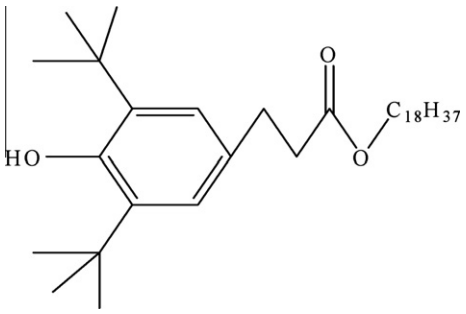

Fig. 1. Formula of Irganox 1076®.

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-

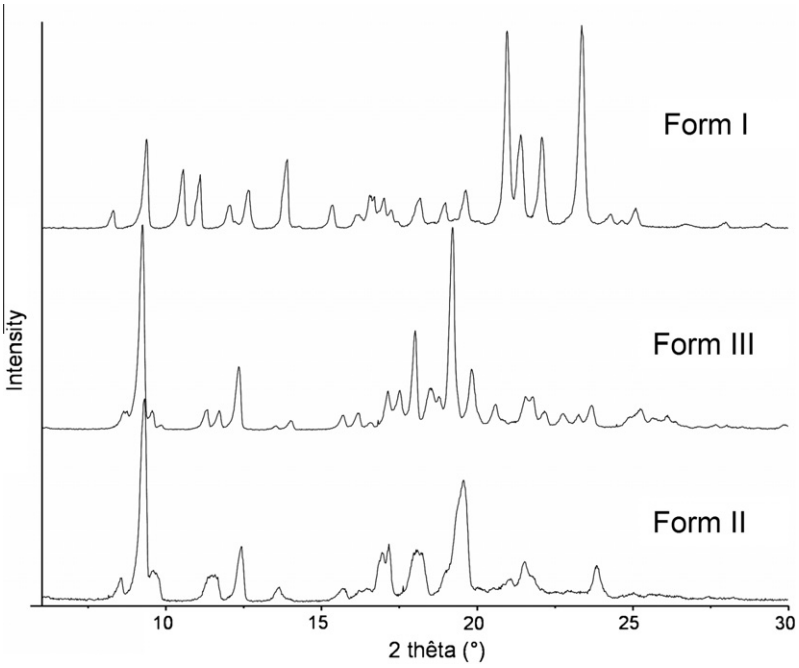

Fig. 2. Diffractogram of the forms I–III.