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Effect of spectroscopic properties on photostability of tamoxifen citrate polymorphs

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Abstract

The photostability of tamoxifen citrate polymorphs, forms A and B, was investigated by chromatographic and spectroscopic analyses including high-pressure liquid chromatography (HPLC), colorimetry and UV/vis solid-state absorption spectroscopy. On the basis of the results of photostability studies under irradiation by visible light and both UVA (320–400 nm) and a fraction of UVB (290–320 nm) light, form A was chemically unstable, whereas form B was stable against light irradiation. The surface color of pellets prepared with any of these crystal forms turned from white to brown; however, the extent of color change in cross-sections of form A pellet was deeper than that of form B pellet. The maximum peak of UV/vis solid-state absorption spectra of form A was observed at 337 nm within the UVA range and was in longer wavelength regions than form B, which exhibited the strong UV absorption mainly in UVB and UVC region. The results obtained suggested that the photodegradation followed by surface color change of form A crystal was caused by the selective absorption of photoenergy of UVA light irradiated by a xenon lamp.

Keywords: Pre-formulation; Solid-state stability; Photostability; Polymorphism; Crystal form; UV/vis spectroscopy

1. Introduction

During the process of drug development, stability has been identified as an essential element to assure the safety and efficacy of drug products because of the possibility of toxic degradants and loss of active ingredient (Yasueda et al., 2004). In particular, the solid-state stability of drug substances in the early stage of drug development would impact on the selection of the solid form, formulation and packaging (Aman and Thoma, 2002; Byrn et al., 2001; Huang and Tong, 2004; Matsuda and Mihara, 1978; Ragno et al., 2003; Waterman and Adami, 2005). The solid-state stability of crystalline drugs is generally classified into various categories, including physical and chemical stability. Physical stability represents the stability in crystalline form, in which the transformation of polymorphs and pseudopolymorphs would occur under some storage conditions relating to humidity and temperature. Chemical stability represents resistance against chemical reactions such as oxidization, dimerization and degradation. It is well known that the polymorphism of drug substances sometimes affects their physical and chemical stability (Gandhi et al., 2000; Matsuda and Tatsumi, 1990; Maurin et al., 2002; Otsuka et al., 1991, 1993), possibly due to differences in molecular arrangement.

Recently, the number of photosensitive drugs has noticeably increased, and articles dealing with the relationship between crystal forms and their photochemical stability have been reported (Akimoto et al., 1985; Glass et al., 2004; Nord et al., 1997; Teraoka et al., 2004). Pellets of three polymorphs of carbamazepine showed different photostability as detected by Fourier-transformed infrared reflection-absorption spectrometry and colorimetry (Matsuda et al., 1994). Pellets of four polymorphs and two pseudopolymorphs of furosemide also showed different photostability as detected by colorimetry and kinetic study of photodegradation was elucidated (De Villiers et al., 1992; Matsuda and Tatsumi, 1990). Thus, the photostability of polymorphs has been investigated to some extent, although

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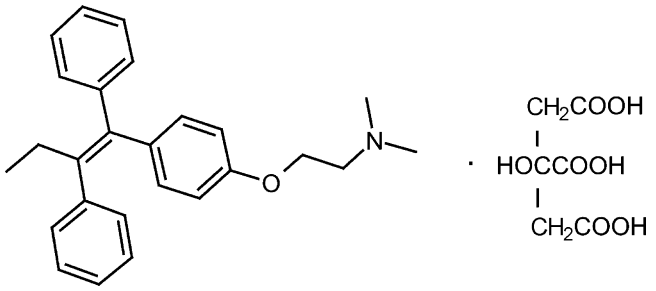

Fig. 1. Chemical structure of tamoxifen citrate.

the relationship between photostability and the physicochemical properties of crystals has not been fully elucidated.

In this paper, we focused on the photodegradation of tamoxifen citrate polymorphs caused by photochemical reaction, and investigated the relationship between photostability and UV/vis solid-state absorption spectra of the crystalline forms. Tamoxifen citrate (Fig. 1), clinically used as an antiestrogenic agent for the treatment of breast cancer (Pappas and Jordan, 2002), exhibits two crystalline forms, A and B (Goldberg and Becker, 1987). Tamoxifen has been also used as a model pharmaceutical compound for preformulation studies and many researches have been conducted (Bhatia et al., 2004; Brigger et al., 2001; Ho et al., 2004; Kojima et al., 2006; Shenoy and Amiji, 2005; Zeisig et al., 2004). Previously, tamoxifen was reported to be a photosensitive drug (Onoue and Tsuda, 2005; Salamoun et al., 1990; Wilson and Ruenitz, 1993), and the color change of tamoxifen citrate used for drug substances under sunlight irradiation was also described in the interview form issued by the manufacturer. We demonstrated solid-state photochemical evaluation of tamoxifen citrate polymorphs, forms A and B. A novel insight into the relationship between photostability and the spectroscopic properties of these crystals was also identified and discussed.

2. Material and methods

2.1. Preparation of polymorphs

Tamoxifen citrate was obtained from EGIS Pharmaceuticals (Budapest, Hungary). All solvents were purchased from Wako Pure Chemical Industries (Osaka, Japan). Tamoxifen citrate form A was a bulk powder purchased from EGIS Pharmaceuticals. Form B was obtained by crystallization from a saturated isopropyl alcoholic solution of the drug with stirring overnight at room temperature. Purity was assessed by RP-HPLC and crystalline forms were identified by powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA).

2.2. High-pressure liquid chromatography (HPLC)

Tamoxifen was analyzed with an HPLC system (Model 510, Waters, Milford, MA, USA) and UV detector (Waters 486, Waters) operated at 205 nm. The packaged column was Inertsil ODS-3 (3 μm, 4.6 mm × 250 mm, GL Science, Tokyo, Japan) operated at 25 °C at a flow rate of 1.0 mL/min. The mobile phase consisted of acetonitrile:10 mM ammonium acetate buffer (80:20). After light irradiation, a powder sample in the glass vial was dissolved in methanol and subjected to an HPLC analysis for purity assessment.

2.3. Powder X-ray diffractometry

Powder X-ray diffraction patterns were recorded using a RINT Ultima (Rigaku, Tokyo, Japan) with Cu Kα radiation generated at 14 mA and 30 kV at room temperature. Data were collected from 2° to 40° (2θ) at a step size of 0.02° and scanning speed of 4° min^{-1}.

2.4. Thermal analysis

DSC was performed using a DSC-3100 system (Mac Science, Tokyo, Japan). The DSC thermogram was obtained from an aluminum open-pan system using a sample weight of ca. 5 mg and a heating rate of 10 °C/min under a nitrogen flow rate of 30 mL/min. TGA was performed using a TG/DTA 2000SA system (Bruker AXS, Madison, WI, USA). The TGA thermogram was obtained under the same conditions as those for DSC.

2.5. UV/vis solid-state spectroscopy

Diffuse reflectance UV/vis solid-state absorption spectra of tamoxifen citrate forms A and B were recorded on a UV-2450 system (Shimadzu, Kyoto, Japan) equipped with an integrating sphere unit (Shimadzu ISR-2200) at room temperature. A quartz cell was filled with sample powder and the spectra were acquired with 1.0 nm sampling pitch in the wavelength range from 190 to 700 nm.

2.6. Preparation of sample pellets

The sample powders were accurately weighed and compressed using an oil hydraulic press (WPM-2, Okada Seiko, Tokyo, Japan) equipped with flat-faced punches and cylindrical die (8 mm i.d.) set at a compression force of 10 kN for 30 s. After compression, crystalline forms of compressed pellets were assessed by PXRD. No polymorphic transformation occurred before and after compression for any of these crystalline forms.

2.7. Irradiation test

The powder and pellets of tamoxifen citrate forms A and B were placed in capped 10 mL glass vials (1.2 mm in thickness) and a six-well cell culture plate (Corning, NY, USA) covered with a glass plate (1.5 mm in thickness), respectively. Samples were stored in a light-irradiation tester (Light-Tron Xenon LTX-01, Nagano Science, Osaka, Japan) equipped with a 2 kW xenon lamp. The spectral irradiation energy of the lamp through an optical filter and infrared cutting filter (Nagano Science) ranged from 310 to 800 nm, with a maximum intensity of 470 nm.

Illuminance was set at 30,000 lx and the irradiation was carried at 25 °C. Illuminance (30,000 lx) was checked on a UVR-2 radiometer (Topcon, Tokyo, Japan) for each experimental procedure.

2.8. Colorimetric measurement

The surface color of the compressed sample pellet was measured with a chromameter (CCR-221, KONICA MINOLTA HOLDINGS, Tokyo, Japan) in the $L^*a^*b^*$ color system. Color difference (ΔE) between the intact and irradiated samples was calculated and all values were the averages of two determinations.

2.9. Statistics

Data for the depth of color changes on cross-section of pellets were expressed as the mean ± S.D. of at least 10 determinations for each experimental group, and were analyzed using Student's *t*-test. Differences were considered significant when $p < 0.01$.

3. Results

3.1. Solid-state photodegradation of form A and B crystals

The photostability test was performed with powder of forms A and B, for which crystalline forms were evaluated by PXRD (Fig. 2), DSC and TGA according to the data reported previously (Goldberg and Becker, 1987). HPLC chromatograms of intact samples indicated that the amount of impurity was extremely small and negligible. The powder in capped 10 mL glass vials was stored under light irradiation by a xenon lamp equipped with a cutting filter ranging from 310 to 800 nm. Polymorphic changes of crystalline forms after irradiation were assessed by PXRD, and no transformation was detected. After chronic light irradiation, each sample was subjected to HPLC analysis, and the purity was assessed and compared (Fig. 3). Several unidentified peaks, eluted within 3–5 min, were detected on HPLC chromatograms after irradiation to form A sample, suggesting that the photodegradation was induced. Without light irradiation, both forms A and B were stable at least during the period tested, because no significant peaks attributable to photoproducts were detected. Exposure of form A to xenon lamp for 30 days resulted in significant decrease of purity as low as 87% (Table 1). On the other hand, form B was quite photostable and the amount of tamoxifen remained 99% even after 30-day exaggerated irradiation. These results suggested that form A was photosensitive, whereas form B was quite resistant to photo-irradiation.

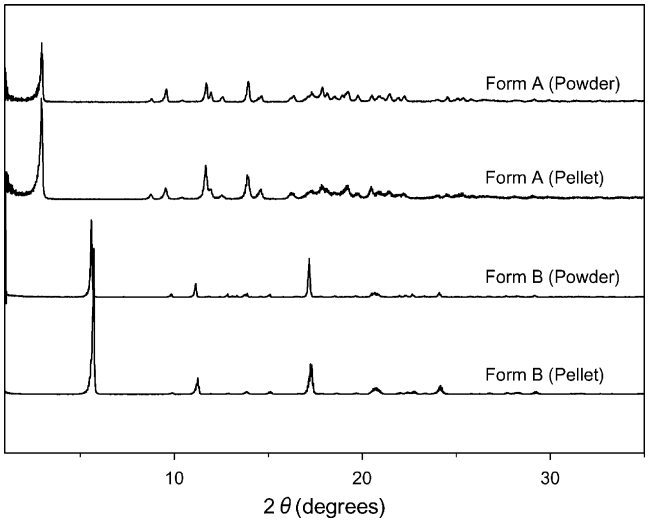

Fig. 2. PXRD patterns of forms A and B for irradiation tests.

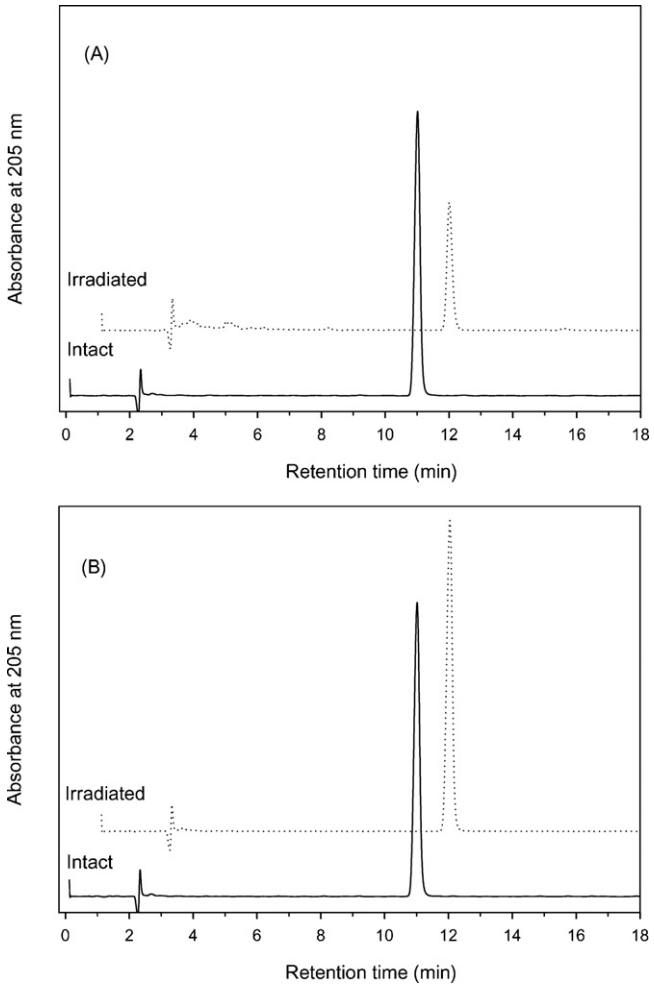

Fig. 3. HPLC chromatograms of forms A (A) and B (B) before irradiation (intact) and after 30-day irradiation (irradiated). Solid line (—), intact sample; dotted line (· · ·), irradiated sample.

Table 1
Photodegradation of tamoxifen citrate forms A and B

Forms	Storage condition	Purity (percentage of total area)			
		Initial	10 days	20 days	30 days
Form A	Non-irradiated	100	99	99	99
	Photo-irradiated	–	94	92	87
Form B	Non-irradiated	100	99	99	100
	Photo-irradiated	–	99	99	100

Each compound was exposed to xenon lamp at the illuminance of 30,000 lx for the indicated periods, then subjected to an HPLC analysis.

Table 2
Color changes of pellets of tamoxifen citrate forms A and B before and after irradiation

Forms	Exposure period	L^*	a^*	b^*	ΔE
Form A	Initial	95.7	−0.3	−3.4	–
	5 days	88.5	−1.8	31.6	35.8
	10 days	85.4	−0.1	38.1	42.8
	20 days	83.2	2.1	43.5	48.6
	30 days	79.3	5.3	48.2	54.5
Form B	Initial	97.4	−0.1	−1.9	–
	5 days	94.5	−2.8	18.3	20.5
	10 days	93.0	−2.2	24.1	26.4
	20 days	90.1	−0.9	30.9	33.6
	30 days	90.9	−0.6	31.0	33.6

The a^* scale for green-red, the b^* scale for yellow-blue, L^* scale for black-white and ΔE for color difference.

3.2. Discoloration of form A and B pellets after light irradiation

The color changes of forms A and B were assessed with pellets prepared from these forms. Polymorphic changes of these crystalline forms after irradiation were assessed by PXRD, and the data obtained clearly showed no polymorphic transformation even after long-term light irradiation. Intact and irradiated samples were subjected to colorimetric measurement to compare the surface color changes of pellets before and after irradiation. The surface color of pellets prepared from form A significantly turned from light white to dark brown upon exposure to light. On the other hand, the surface color of form B pellets gradually turned from light white to light brown. Color changes before and after irradiation were evaluated by two chromaticness coordinates (a^* scale for green-red and b^* scale for yellow-blue), the illuminance coordinate (L^* scale for black-white) and color difference (ΔE) before and after irradiation (Table 2). Although the a^* scale of both crystal forms was almost invariable, the L^* and b^* scales remarkably decreased (turned to black) and increased (turned to yellow) after the elapsed irradiation time, respectively. Thus, changes in the $L^*a^*b^*$ system suggested that forms A and B turned to brown. The ΔE values of forms A and B after 30-day irradiation increased up to 54.5 and 33.6, respectively. The ΔE value of form A was much greater than that of form B at any irradiation time, suggesting that form A discolored more sensitively as compared to form B.

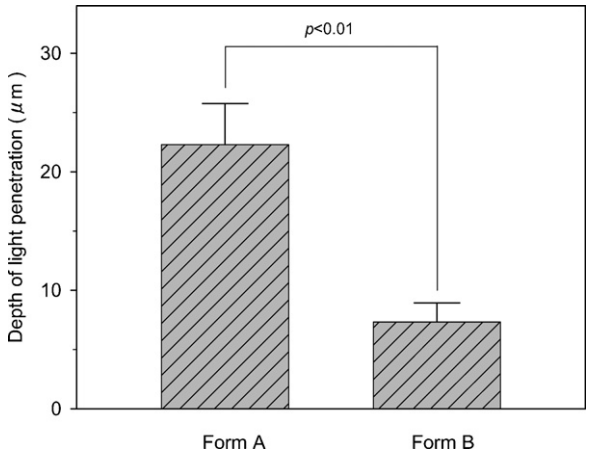

Fig. 5. Depth of light penetration measured as color changes in the cross-sections of forms A and B pellets. Each column represents the mean ± S.D. of at least 10 determinations for each experimental group. Significantly different between forms A and B; $p < 0.01$.

The thickness of the discoloration layer was assessed in cross-sections of form A and B pellets. After colorimetric measurement of the pellet surface, the pellets were cut with a razor for microscopic observation of cross-sections. The similar void ratio of these pellets, obtained from the apparent densities of pellets and particle densities of forms A and B, should result in a depth of color change corresponding to light penetration. The depth of color changes on cross-sections of pellets, as a measure for light penetration into the pellets, was measured and the results are shown in Fig. 4. The color of cross-sections of pellets prepared from forms A and B turned from light white to dark brown and light brown upon exposure to UV light, respectively. The depth of the discolored layer in cross-sections of form A and B pellets after 30-day irradiation was 22.3 ± 3.5 and 7.3 ± 1.6 μm, respectively ($p < 0.01$) (Fig. 5). These results suggested that light penetration was far deeper in form A pellets than form B pellets, irrespective of the same porosity.

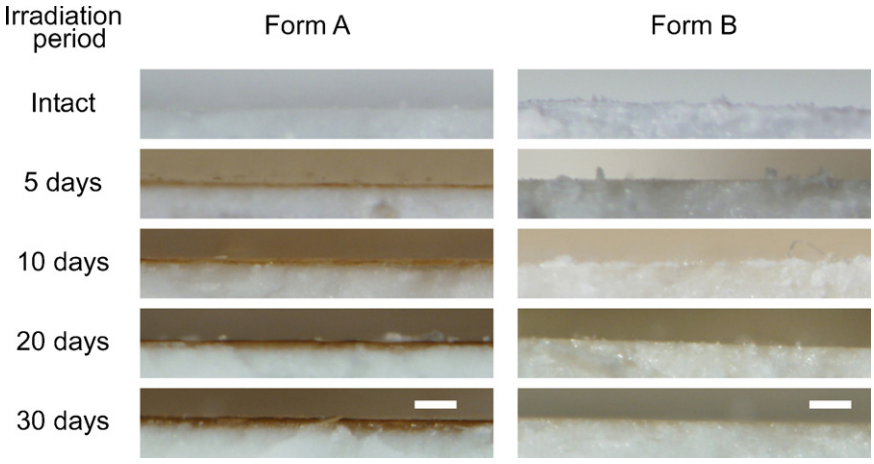

Fig. 4. Photomicrographs of cross-sections of form A and B pellets under UV light irradiation for 5, 10, 20 and 30 days. Scale bar represented 100 μm.

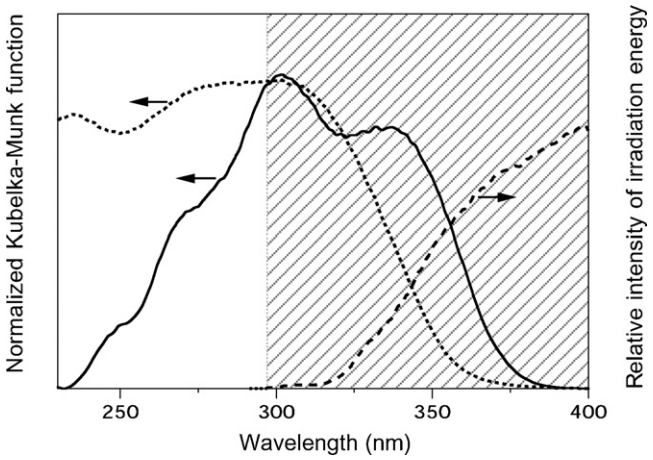

Fig. 6. Ultraviolet absorption spectra of forms A and B. Solid line (—), form A; dotted line (···), form B; broken line (- - -), xenon lamp. Hatched region; irradiation wavelength range by xenon lamp.

3.3. Spectroscopic properties of form A and B crystals

The photostability of solid pharmaceutical substances depends on many factors, i.e., surface area and photochemical properties of the sample, and the irradiation conditions such as spectral irradiation energy and even type of the light source. Although most of these parameters can be controlled, the photochemical properties of samples are uncontrollable, because these are the intrinsic properties depending on the molecular structure. In this study, the solid-state absorption spectra in the UV/vis region were investigated in order to elucidate the relationship between photostability and photochemical properties. Diffuse reflectance UV/vis solid-state absorption spectra of forms A and B were recorded on a spectrophotometer equipped with an integrating sphere unit at room temperature, and compared with the spectral irradiation intensity pattern of a xenon lamp to assess the absorbability of photoenergy by these crystals (Fig. 6). In this figure, the maximum values of Kubelka–Munk function for forms A and B are modified so as to be equal to easily enable qualitative comparison of difference in spectra of these forms and spectral irradiation pattern simulating sunlight. The irradiation light passing through a filter (310–800 nm) was composed of visible light (>400 nm), UVA (320–400 nm) and a fraction of UVB (290–320 nm). Form B exhibited the strong UV absorption mainly in the UVB and UVC region. In contrast, the maximum peak absorption of form A was clearly observed at 337 nm in the UVA range and was at a longer wavelength (bathochromic shift) than form B. On the basis of the photostability data, these results suggested that form A would absorb much more photoenergy than form B, resulting in easier photoexcition and the formation of photoproducts upon exposure to UVA light.

4. Discussion

We have demonstrated for the first time that the difference in photostability between tamoxifen citrate polymorphs, forms A and B is associated with their spectroscopic properties, solid-state UV/vis absorption spectra, due to different molecular arrangements in the crystal lattice. According to the data shown in Tables 1 and 2, we revealed that form A was unstable, whereas form B was stable under photo-irradiation. The results of the UV/vis solid-state absorption spectra of these crystal forms showed that the maximum absorption peak was observed at 337 nm in the UVA range for form A and was at a longer wavelength than form B which exhibited the strong UV absorption mainly in the UVB and UVC region. The wavelength of light radiated from a xenon lamp ranged from 310 to 800 nm, composed of visible light, UVA (320–400 nm) and a fraction of UVB (290–320 nm). Taking these results into account, the photoinstability and depth of color changes of form were caused by the selective absorption of photoenergy of UVA light radiated by a xenon lamp.

Under light irradiation, drug molecules absorb photon energy and molecules are excited in the singlet state. The excitation energy in the singlet state is generally dissipated as fluorescence, heat or exhausted in photochemical reactions caused by reactive oxygen spices such as singlet oxgen ($^1O_2$) and superoxide (O_2^-) generated from photo-irradiated substances (Onoue and Tsuda, 2005). Different crystal structures due to polymorphism should exhibit different energy states. Recently, the differences of solid-state fluorescence as a photophyisical property among polymorphs were discussed and elucidated (Brittain et al., 2005; Kaczmarek and Kaczmarski, 1996). Apart from these researches, we investigated the solid-state photoreaction, which possibly affects the photostability of polymorphs. However, to the best of our knowledge, the relationship between photostability and the photophysical properties of crystal forms was not elucidated.

With respect to UV/vis spectroscopy in solution, the maximum absorption spectra band shifted to longer or shorter wavelengths depending on the condition, such as dissolving solvents, which was called solvent shift, caused by solvent–solute interaction due to the dipole moment transformation of chromophore during excitation (Naseem et al., 2004; Verdasco and Martín, 1995). Recently, attention has also been drawn to the solid-state absorption spectra band shift (Aman and Thoma, 2003; Mizuguchi et al., 1995; Stockton et al., 1998). In the solid state, the absorption spectra band shift is caused by intra/intermolecular interaction, which may depend on its crystal packing surrounded by chromophores during excitation. Thus, this polymorphism could be dominant for the absorption spectra in the solid state.

Tamoxifen was known as a photosensitive drug and generate superoxide after UVA/UVB irradiation (Onoue and Tsuda, 2005). It was also reported that tamoxifen was photochemically converted into phenanthrene derivative under UV irradiation in the solution state (Salamoun et al., 1990). We have conducted the solid-state photostability studies on tamoxifen citrate and demonstrated that form A was photosensitive and the different photosensitivity among polymorphs was caused by specific UV/vis solid-state absorption spectra, probably depending on crystal packing surrounded by chromophores during excitation. In drug development, photosensitivity impacts on the formulation, manufacturing process, packaging and storage conditions. Information about the photosensitivity of solid drug substances

could make it possible to reduce development costs. Based on the results of this study, form B could be said to be a suitable form for reasonable development from the viewpoint of medical economics.

In conclusion, we have provided a novel insight into the photosensitivity of tamoxifen citrate polymorphs. We also demonstrated that solid-state absorption spectra could be used as a useful method for the photophysical characterization of polymorphs. In the development of photosensitive drug substances, solid-state absorption spectra may provide key information about photosensitivity.

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