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International Journal of Pharmaceutics 352 (2008) 146–151
INTERNATIONAL JOURNAL OF PHARMACEUTICS
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Physicochemical properties of tamoxifen hemicitrate sesquihydrate

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Received 2 June 2007; received in revised form 5 September 2007; accepted 21 October 2007
Available online 26 October 2007

Abstract

A novel modification of tamoxifen [(*Z*)-2-[4-(1,2-diphenyl-1-butenyl) phenoxy]-*N*,*N*-dimethylethylamine] citrate, tamoxifen hemicitrate hydrate was prepared. The crystalline form was identified and characterized by powder and single crystal X-ray diffractometries, differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), and hot-stage microscopy, and its physicochemical stability was also evaluated. The results of an elemental analysis, a single crystal X-ray analysis, and the TGA suggested that the molar ratio of tamoxifen:citric acid:water was 2:1:3 indicating it to be tamoxifen hemicitrate sesquihydrate. Simultaneous XRD–DSC measurements also indicated that two hydrates, sesquihydrate and hemihydrate, and an anhydrous form would exist during heating. The physicochemical stability of tamoxifen citrate forms A and B suspended in water and of form A during kneading and drying suggested that tamoxifen citrate was transformed into tamoxifen hemicitrate hydrate in water within 24 h, whereas tamoxifen citrate in a mixture with microcrystalline cellulose was quite stable during kneading. These results suggested that water and a mixture of water and organic solvent should be used for the manufacturing process with special attention paid to the transformation to tamoxifen hemicitrate sesquihydrate, because it showed a different stoichiometry from the active ingredient, tamoxifen citrate.

Keywords: Tamoxifen; Hydrate; Physicochemical characterization; Physicochemical stability

1. Introduction

The solid-state characterization of crystal forms of drug candidates is important to the process of pharmaceutical development. Notably, research on hydrates is essential since their physicochemical properties provide not only information for understanding the behavior of drugs in the gastrointestinal tract (Hoelgaard and Moeller, 1983; Poole et al., 1968) but also the information for making a suitable decision regarding the manufacturing process, storage conditions, and package design of the drug substance and product (Otsuka et al., 1991; Zhu et al., 1996). Therefore, the screening and characterization of hydrates (Khankari et al., 1998; van Tonder et al., 2004) are often conducted at the early stages of drug development.

Once the hydrate of a drug candidate has been identified, manufacturing risk management such as transformation to the hydrate or anhydrate during the crystallization and formulation processes should be examined. Recently, solid-state transformations during pharmaceutical manufacturing processes such as wet granulation, drying and compression have received attention (Jorgensen et al., 2002; Morris et al., 2001; Otsuka et al., 1995). Theophylline anhydrate was transformed into theophylline monohydrate during wet granulation (Airaksinen et al., 2003). In addition, the possibility of transformation to a theophylline metastable form from the monohydrate during the drying process was indicated (Morris et al., 2001). The transformation of piroxicam from needle-like α-phase crystals into cubic β-phase crystals during compression was also reported (Ghan and Lalla, 1992).

Tamoxifen, (*Z*)-2-[4-(1,2-diphenyl-1-butenyl) phenoxy]-*N*,*N*-dimethylethylamine, is a selective estrogen receptor modulator, and tamoxifen citrate is widely used as a drug for the treatment of breast cancer. Tamoxifen has also been

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doi:10.1016/j.ijpharm.2007.10.021

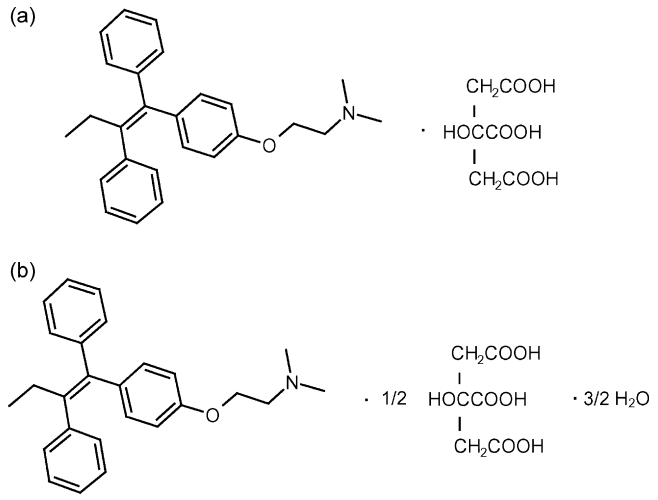

Fig. 1. Chemical structure of tamoxifen citrate (a) and tamoxifen hemicitrate sesquihydrate (b).

used as a model pharmaceutical compound for preformulation studies (Bhatia et al., 2004; Brigger et al., 2001; Ho et al., 2004; Kojima et al., 2006; Shenoy and Amiji, 2005; Zeisig et al., 2004). As for tamoxifen citrate (Fig. 1), two polymorphs, forms A and B, and two pseudopolymorphs, methanolate and ethanolate, have been identified (Goldberg and Becker, 1987; Kojima et al., 2007a,b). In addition, we discovered a novel hydrate of tamoxifen hemicitrate, which was transformed from the anhydrous form of tamoxifen citrate. Even though tamoxifen citrate is widely used all over the world, no investigation of its hydrate has been reported to the best of our knowledge.

In this study, we prepared a novel hydrate of tamoxifen hemicitrate. Its crystal form was identified and characterized by elemental analyses, powder and single crystal X-ray diffractometries, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), simultaneous XRD–DSC, and hot-stage microscopy, and the conditions for transformation to the hydrate were also examined. In addition, the possibility of transformation to the hydrate from tamoxifen citrate during the manufacturing process was discussed.

2. Materials and methods

2.1. Preparation of modifications

Tamoxifen citrate was obtained from EGIS Pharmaceuticals (Budapest, Hungary). All solvents were purchased from Wako Pure Chemical Industries (Osaka, Japan). Form A was a bulk powder purchased from EGIS Pharmaceuticals. Form B was prepared by a method reported previously (Kojima et al., 2007a). The hydrate was obtained by recrystallizing from saturated aqueous solutions of the drug with stirring overnight at room temperature, then filtered and dried in a nitrogen atmosphere.

2.2. Elemental analysis

The elemental analysis was performed on an Elementar Vario EL (Elementar Instrument, Germany) with helium (200 mL/min) as the carrier gas.

2.3. Powder and single crystal X-ray diffractometries

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

Single crystal X-ray diffraction data were recorded on a RAXIS-RAPID (Rigaku, Tokyo, Japan) with Cu Kα radiation at −183 °C. The crystal structure was solved and refined using SHELX97 software (Sheldrick, 1997).

2.4. Thermal analysis

DSC was performed using a DSC 6200 system (Seiko Instruments, Chiba, Japan). The DSC thermogram was obtained in an aluminum open-pan system using a sample weight of ca. 3 mg and a heating rate of 5 °C/min in a nitrogen flow. TGA was performed using a TG/DTA 6200 system (Seiko Instruments). The TGA thermogram was obtained under the same conditions as those for DSC.

Simultaneous XRD–DSC measurements were performed using RINT Ultima III with DSC attachment +HUM (Rigaku, Tokyo, Japan) with Cu Kα radiation generated at 40 kV and 50 mA at a heating rate of 2 °C min^{-1} in a nitrogen flow. Data were collected within the diffraction angle range of 2–40° (2θ) at a step size of 0.02° and a scanning speed of 28.8° min^{-1}.

Thermal changes of crystal morphology were observed on a hot-stage microscope (LK-FDCS, Linkam Scientific Instruments, Surrey, UK) with a heating rate of 10 °C min^{-1} in a nitrogen flow.

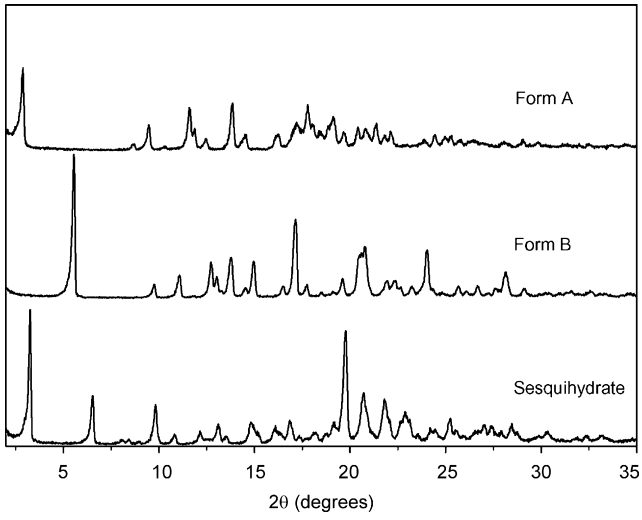

Fig. 2. PXRD patterns of forms A and B, and the hydrate.

Table 1
Elemental analyses of forms A and B, and the hydrate

Crystalline form	Formula	Elemental analysis (%): calcd. (found)		
		C	H	N
Form A	$C_{26}H_{29}NO{\cdot}C_6H_8O_7$	68.19 (67.98)	6.62 (6.54)	2.49 (2.29)
Form B	$C_{26}H_{29}NO{\cdot}C_6H_8O_7$	68.19 (68.04)	6.62 (6.56)	2.49 (2.30)
Sesquihydrate	$C_{26}H_{29}NO{\cdot}0.5C_6H_8O_7{\cdot}1.5H_2O$	70.42 (70.70)	7.34 (7.16)	2.83 (2.66)

2.5. Physicochemical stability of suspended modifications in water

The physicochemical stability of aqueous suspensions of forms A or B was evaluated by PXRD. Form A or B was suspended in water at a concentration of 5 mg/mL at 37 °C for 24 h. Suspension samples were filtrated and subjected to PXRD analysis.

2.6. Physicochemical stability during kneading and after drying

The wet massing method was performed using a pestle and mortar. Tamoxifen citrate form A (10 mg) and microcrystalline cellulose (190 mg) were blended, a different amount of purified water was added, and the mixture was kneaded for 5 min. Then, massed samples were stored for 1 h and subsequently dried at 40 °C under reduced pressure for 2 h. Crystalline forms after wet granulation and drying were evaluated by PXRD. Transformation was confirmed to have occurred based on the characteristic peaks of form A and the hydrate at 2.9 and 3.3° (2θ), respectively.

3. Results and discussion

3.1. Stoichiometry of modifications

Elemental analyses were performed to identify the stoichiometry of forms A and B, and the hydrate crystals. The results indicated that the molar ratio of tamoxifen:citric acid for forms A and B was 1:1, whereas that for the hydrate was 2:1 (Table 1). These results suggested the tamoxifen citrate crystallized from water to be a kind of hydrate of tamoxifen hemicitrate that could not be classified as a pseudopolymorph because of a different stoichiometry from tamoxifen citrate. The results of the elemental analysis also suggested that the molecular ratio of tamoxifen to water for the hydrate was 2:3 and thus the new modification could be identified as tamoxifen hemicitrate sesquihydrate (Fig. 1).

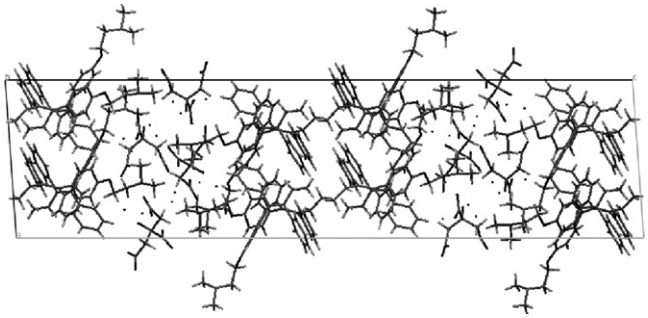

Fig. 3. Crystal structure of the hydrate.

3.2. Powder and single crystal X-ray diffraction analyses

Powder X-ray diffraction (PXRD) patterns of crystal forms are shown in Fig. 2. The characteristic diffraction peaks of forms A and B and significant differences between them were observed and PXRD patterns agreed well with the data reported previously (Goldberg and Becker, 1987; Kojima et al., 2007a). The characteristic X-ray diffraction peaks of tamoxifen hemicitrate sesquihydrate were observed at 3.3, 6.5, 9.8 and 19.8° (2θ). The crystal structure of the sesquihydrate was analyzed by single crystal X-ray diffractometry. The results indicated that the sesquihydrate was triclinic ($a = 13.7939(3)$, $b = 14.3500(3)$, $c = 53.5812(15)$ Å, $\alpha = 84.7570(18)$, $\beta = 85.0890(18)$, $\gamma = 79.358(2)°$), space group P-1 ($Z = 8$, density = 1.269 g/cm^3, $R_1 = 0.1292$). The results of the single crystal analysis of the sesquihydrate also indicated that the molar ratio of tamoxifen:citric acid:water was 2:1:3 and identified the form as tamoxifen hemicitrate sesquihydrate, which coincided with the results of the elemental analysis (Fig. 3). Water molecules were all positioned among citric acid molecules with hydrogen bonds and would play an important role in the stabilization of the crystals consisted of tamoxifen hemicitrate. These results suggested that the crystals whose stoichiometry of tamoxifen:citric acid was 2:1 were only obtained by crystallization from water.

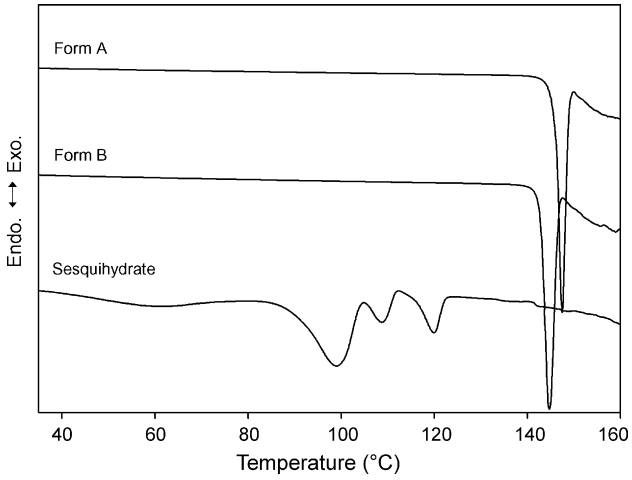

Fig. 4. DSC thermograms of forms A and B, and the hydrate.

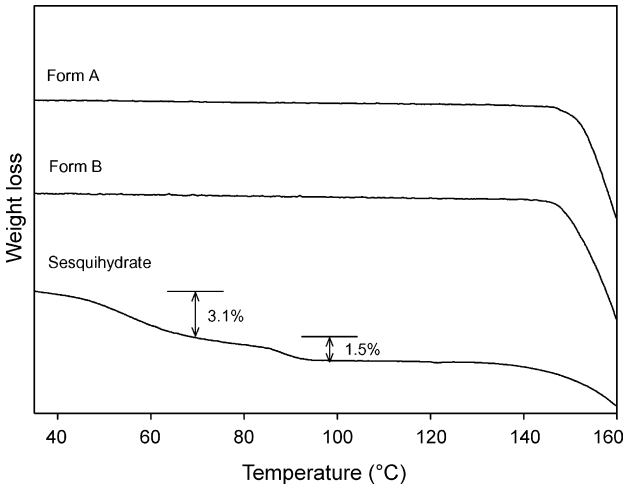

Fig. 5. TGA thermograms of forms A and B, and the hydrate.

3.3. Thermal properties

The thermal behavior of tamoxifen hemicitrate sesquihydrate was evaluated by using DSC and TGA. The DSC curve seemed to show a broad endothermic peak at 62.2 °C and two subsequent peaks at 99.6 and 109.2 °C, an exothermic peak at 112.7 °C, and then an endothermic peak due to melting at 120.3 °C, quite different thermal behavior from forms A and B (Fig. 4). The TGA thermogram suggested that two steps of dehydration, indicating the existence of two hydrates, sesquihydrate and hemihydrate, occurred with a weight loss of 3.1 and 1.5%, respectively, corresponding to the endothermic peaks of DSC thermogram (Fig. 5). The TGA thermogram also suggested that the molar ratio of tamoxifen hemicitrate:water was in 2.0:2.6 and the water content was smaller than the theoretical ratio (2.0:3.0). Dehydration would occur under dry nitrogen before the thermogram was recorded during the TG/DTA measurement.

To identify the potential of the two crystalline forms of the hydrate indicated by the results of DSC and TGA, the relationship between PXRD and DSC was made clear by using simultaneous measurements of DSC and PXRD during heating at a rate of 2 °C min^{-1} (Fig. 6). The characteristic X-ray diffraction peak at 19.8° (2θ) of tamoxifen hemicitrate sesquihydrate (Fig. 2) on the PXRD pattern at 32.0–33.8 °C disappeared and a new peak at 20.2° (2θ) appeared at 79.8–82.9 °C with a broad endothermic peak detected by DSC (Fig. 4). The characteristic X-ray diffraction peak at 20.2° (2θ) also disappeared and then a separate new peak at 19.5° (2θ) appeared at 98.7–101.8 °C with an endothermic peak. These results suggested tamoxifen hemicitrate to have two hydrates, sesquihydrate and hemihydrate, and an anhydrous form showing PXRD patterns at 32.0–33.8, 79.8–82.9 and 98.7–101.8 °C in Fig. 6, respectively. Tamoxifen hemicitrate sesquihydrate would change to hemihydrate with the first dehydration, and subsequently to the anhydrous form with the second dehydration. The gradual decrease in the X-ray diffraction intensity of the anhydrous form above 117.6 °C indicated that the crystallinity decreased with the melting of the anhydrous form. During the melting event, slight crystallization with a characteristic peak at 14.2° (2θ) on the PXRD pattern at 117.6–120.6 °C was observed. The results of microscopic observation on the hot-stage also proved that slight crystallization occurred during melting. The DSC thermogram exhibited two endothermic peaks and one exothermic peak at 109.2, 120.3 and 112.7 °C, respectively (Fig. 4). A broad endothermic peak between 105 and 125 °C corresponding to the melting of the anhydrous form and an exothermic peak at 110 °C corresponding with crystallization could result in apparent peaks, thus recording two endothermic peaks at 109.2 and 120.3 °C and an exothermic peak at 112.7 °C on the DSC themogram.

3.4. Effects of crystallization, kneading and drying processes on the crystal form

The physicochemical stability of forms A and B suspended in water at a concentration of 5 mg/mL at 37 °C was evaluated. The PXRD patterns suggested that both forms A and B of tamoxifen citrate were transformed into tamoxifen hemicitrate sesquihydrate within 24 h (Fig. 7). The metastable form A was completely transformed into sesquihydrate, whereas the stable form B was only partially transformed. We have previously demonstrated that both forms were quite stable at least for 2 months even under severe storage conditions at 97% RH at 40 and 60 °C and

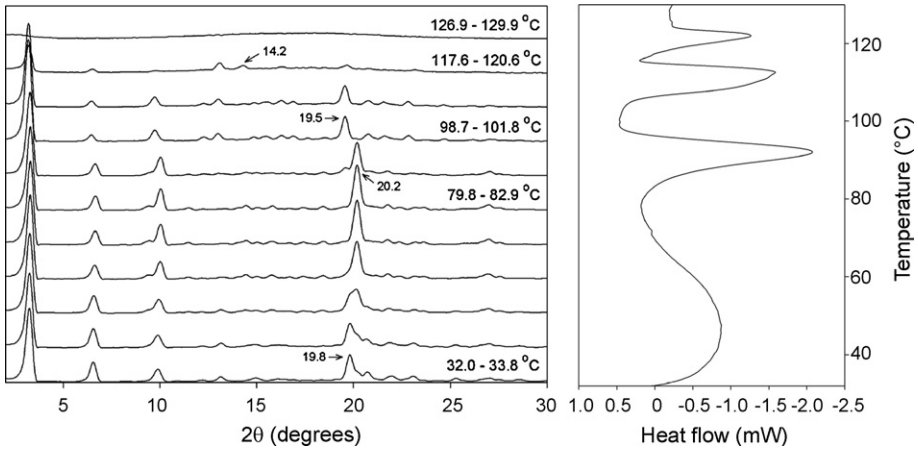

Fig. 6. Relationship between the PXRD patterns and DSC thermogram of the hydrate.

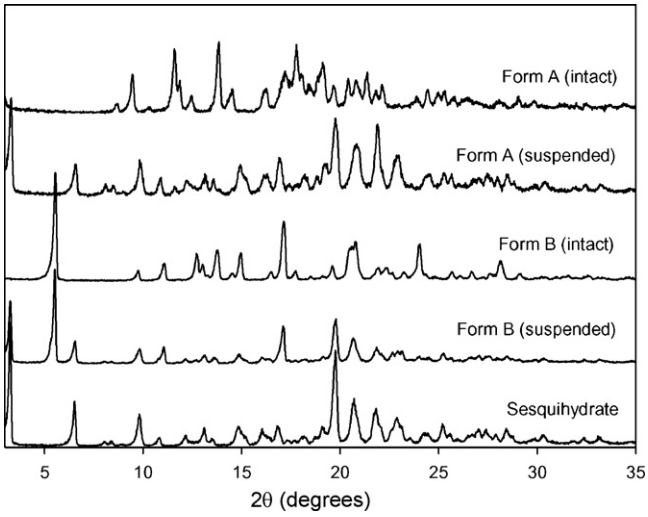

Fig. 7. PXRD patterns of tamoxifen citrate forms A and B, their suspended samples and sesquihydrate.

no transformation was observed. These results suggested that the transformation to the sesquihydrate would be a water-mediated one.

To the best of our knowledge, few studies on changes of stoichiometry from the viewpoint of the pharmaceutical manufacturing process have been reported (Alejska and Wiewiorowska, 1994; Trask et al., 2005). The solvent-drop grinding of an ingoing 2:1 caffeine/maleic acid ratio with methanol addition produces cocrystal product with a stoichiometry of 1:1 with excess caffeine. Whereas, the solvent-drop grinding of an ingoing 1:1 material with toluene provides cocrystal product with a stoichiometry of 2:1 with excess maleic acid and some unreacted residual caffeine as a minor component (Trask et al., 2005). We have described one of the few cases where tamoxifen citrate was transformed into tamoxifen hemicitrate sesquihydrate with a change of stoichiometry of salt in water.

Recently, the transformation of polymorphs and hydrate during the manufacturing of drug products has attracted attention (Airaksinen et al., 2003; Morris et al., 2001; Otsuka et al., 1995). Notably, careful attention should be paid to the wet granulation and subsequent drying processes, since wet granulation could induce transformation from the metastable form to the hydrate or the stable form and conversely drying could induce transformation from the hydrate to anhydrous form. To assure stability during these manufacturing processes, kneading of the mixed powder of tamoxifen citrate form A and microcrystalline cellulose (1:19), the adding of different amounts of purified water, storage, and then drying were performed (Table 2). The PXRD patterns of the sample kneaded for 5 min suggested no transformation to the hydrate and that form A was quite stable during kneading (wet granulation). During the storage and drying process, the crystalline form change was also not observed. These results indicated that the amount of water used for kneading could not induce the water-mediated transformation to the hydrate.

Table 2
Effects of kneading and drying processes on the crystalline form of tamoxifen citrate

Amount of water added to dry mixture[a] (g/g)	After kneading	After drying
0	Form A	Form A
0.25	Form A	Form A
0.50	Form A	Form A
1.00	Form A	Form A

[a] Tamoxifen citrate form A:microcrystalline cellulose (1:19).

Water is an acceptable solvent for the pharmaceutical manufacturing of drug substances. In the pharmaceutical manufacturing process, pure water or a binary mixture of some organic solvent and water could be available for salt formation and crystallization as the final step in the synthesis of a drug substance. Notably, water has been often used for wet granulation. From the results described above, tamoxifen citrate would not be transformed into tamoxifen hemicitrate hydrate during pharmaceutical manufacturing processes such as wet granulation, however it could change to the hydrate during manufacturing processes of drug substance such as salt formation and crystallization. These results suggested that the solvent for salt formation and crystallization should be selected with attention to transformation to tamoxifen hemicitrate sesquihydrate having a different stoichiometry from the active ingredient, tamoxifen citrate.

4. Conclusion

We have provided novel insight into tamoxifen citrate modification, tamoxifen hemicitrate sesquihydrate. The results of the elemental analysis, single crystal X-ray analysis, and TGA revealed that the molar ratio of tamoxifen:citric acid:water was 2:1:3 and indicated that the new modification would be tamoxifen hemicitrate sesquihydrate. Simultaneous XRD–DSC measurements also indicated that two hydrates, sesquihydate and hemihydrate, and an anhydrous form would exist during heating.

We have also demonstrated the physicochemical stability of tamoxifen citrate forms A and B suspended in water and the physicochemical stability of form A during kneading and drying. Tamoxifen citrate suspended in water was transformed into a hydrate within 24 h, whereas tamoxifen citrate in a mixture with microcrystalline cellulose was quite stable during kneading.

Tamoxifen citrate could be transformed into tamoxifen hemicitrate sesquihydrate with the change of the stoichiometry of salt during manufacturing processes such as salt formation and crystallization. To the best of our knowledge, very few studies on changes of stoichiometry have been reported and discussed from the viewpoint of the manufacturing process. Therefore, a thorough understanding of the physicochemical properties of modifications of drug substances is necessary for rational pharmaceutical development, since unexpected changes in the potency of the active ingredient could be caused by a change of stoichiometry during the manufacturing process.

Acknowledgements

We wish to thank Motoo Shiro and Akira Kishi, Rigaku corporation for the single crystal X-ray analysis and simultaneous XRD–DSC measurement.

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