International Journal of Pharmaceutics 460 (2014) 83–91

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Four new polymorphic forms of suplatast tosilate

Keiko Nagai[a,e,*], Takanori Ushio[b], Hidenori Miura[c], Takashi Nakamura[d], Kunikazu Moribe[e], Keiji Yamamoto[e]

[a] Taiho Pharmaceutical Co. Ltd., Ebisuno, Hiraishi, Kawauchi-cho, Tokushima 771-0194, Japan
[b] Ace Japan Co. Ltd., Higashine-koh, Higashine, Yamagata 999-3701, Japan
[c] Taiho Pharmaceutical Co. Ltd., Kamikawa-machi, Kodama-gun, Saitama 367-0241, Japan
[d] RIKEN, Wako, Saitama 351-0198, Japan
[e] Graduate School of Pharmaceutical Sciences, Chiba University, Inohana, Chuo-ku, Chiba 260-8675, Japan

ARTICLE INFO

Article history:
Received 16 August 2013
Received in revised form 20 October 2013
Accepted 29 October 2013
Available online 6 November 2013

Keywords:
Suplatast tosilate
Polymorphs
Seeding analogous compounds
Physicochemical properties
Solubility
Rietveld refinement

ABSTRACT

We found four new polymorphic forms (γ-, ε-, ζ-, and η-forms) of suplatast tosilate (ST) by recrystallization and seeding with ST-analogous compounds; three polymorphic forms (α-, β-, and δ-forms) of ST have been previously reported. The physicochemical properties of these new forms were investigated using infrared (IR) spectroscopy, solid-state nuclear magnetic resonance (NMR) spectroscopy, differential scanning calorimetry, and powder X-ray diffractometry. The presence of hydrogen bonds in the new forms was assessed from the IR and solid-state NMR spectra. The crystal structures of the ε- and η-forms were determined from their powder X-ray diffraction data using the direct space approach and the Monte Carlo method, followed by Rietveld refinement. The structures determined for the ε- and η-forms supported the presence of hydrogen bonds between the ST molecules, as the IR and solid-state NMR spectra indicated. The thermodynamic characteristics of the seven polymorphic forms were evaluated by determining the solubility of each form. The α-form was the most insoluble in 2-propanol at 35 °C, and was thus concluded to be the most stable form. The ε-form was the most soluble, and a polymorphic transition from the ε- to the α-form was observed during solubility testing.

1. Introduction

Polymorphism has long been a subject of great concern in the pharmaceutical industry because different solid pharmaceutical forms can impart different physical and chemical properties that can occasionally affect the bioavailability, dissolution rate, stability, and manufacturability of solid dosage forms (Brittain, 2012; Grunenberg et al., 1996; Jones, 1997; Kawakami, 2007; Thirunahari et al., 2010; Yamamoto et al., 2011). The characterization of solid pharmaceuticals is therefore very important to ensure that pharmaceuticals with standardized qualities are supplied to the consumer. There have been many studies in which solid pharmaceuticals have been physicochemically characterized, and techniques such as differential scanning calorimetry (DSC), infrared (IR) spectroscopy, microscopy, powder X-ray diffractometry (PXRD), Raman spectroscopy, and solid-state nuclear magnetic resonance (NMR) spectroscopy have been used (Ikeda et al., 2010; Tozuka et al., 2002). Most polymorphs can be identified using these analytical techniques, but some polymorphs are still difficult to identify.

Polymorphism is defined as the occurrence of different arrangements and/or conformations of molecules within the crystal lattice. Elucidating the arrangement and/or conformation of the molecules is often crucial to understanding the solid-state chemistry of active pharmaceutical ingredients.

The crystal structure is one of the most crucial pieces of information relating to polymorphism; however, it is not always possible to determine the crystal structure of a metastable crystalline form because single crystals that are suitable for X-ray crystallographic analysis may be unavailable. Such difficulties have recently been overcome by advances in the procedures available for solving structures from powder X-ray diffraction data measured using laboratory X-ray sources (Engel et al., 1999; Harris et al., 1994, 2001; Neumann, 2003; Rietveld, 1969; Stephenson, 2000; Young and Ed, 1993), although there still are some limitations.

Suplatast tosilate (ST) [(±)-[2-[4-(3-ethoxy-2-hydroxypropoxy) phenylcarbamoyl]ethyl]dimethylsulfonium *p*-toluenesulfonate] is an excellent IgE antibody production suppressor, and is a useful therapeutic agent for various allergic diseases. ST is a glycerol

* Corresponding author at: Taiho Pharmaceutical Co. Ltd., Ebisuno, Hiraishi, Kawauchi-cho, Tokushima 771-0194, Japan. Tel.: +81 88 665 3571; fax: +81 88 665 7225.
E-mail address: kei-nagai@taiho.co.jp (K. Nagai).

0378-5173/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ijpharm.2013.10.049

derivative with one chiral carbon atom, which has been developed as a racemate.

It has been reported that changing the crystallization conditions, such as the solvent(s) and temperature, pseudo-seeding the supersaturated solution with a crystal with the desired structure (following an epitaxy protocol), or adding impurities or additives to inhibit the nucleation and/or crystal growth of an undesired polymorph can be used to give a desired polymorph (Maruyama and Ooshima, 2000; Blagden et al., 1998). Using this technique, polymorphs of ST and ST analogous compounds were also prepared (Takahashi et al., 1998a, 1998b, 2002; Tamura et al., 1997, 1998, 2001a, 2001b, 2011).

Three polymorphic forms (α-, β-, and δ-forms) of ST were previously reported, and their crystal structures were determined (Miura et al., 2003; Takahashi et al., 2001; Ushio et al., 1996a, 1996b, 1996c, 2002; Ushio and Yamamoto, 1994). We have found four new polymorphic forms (γ-, ε-, ζ-, and η-forms) by recrystallizing and seeding with ST-analogous compounds.

We investigated the physicochemical properties of the new polymorphic forms of ST by DSC, IR and solid-state NMR spectroscopies, and PXRD. We also determined the solubilities of the new polymorphic forms, and compared them with the solubilities of the three crystals that were previously characterized.

We determined the crystal structures of the ε- and η-forms from their PXRD data using the direct space approach in conjunction with the Monte Carlo method, followed by Rietveld refinement.

2. Materials and methods

2.1. Materials

Suplatast tosilate [(±)-[2-[4-(3-ethoxy-2-hydroxypropoxy) phenylcarbamoyl]ethyl] dimethylsulfonium *p*-toluenesulfonate] (1a), which has been developed as a racemate, was provided by Taiho Pharmaceutical Co. Ltd. (Tokyo, Japan). Analogous compounds of ST, (±)-[2-[4-(3-propoxy-2-hydroxypropoxy) phenylcarbamoyl]ethyl]dimethylsulfonium *p*-toluenesulfonate (1b) and (±)-[2-[4-(3-ethoxy-2-hydroxypropoxy)phenylcarbamoyl]ethyl]trimethylammonium *p*-toluenesulfonate (2), were provided by the Graduate School of Human and Environmental Studies, Kyoto University (Japan), and Taiho Pharmaceutical Co. Ltd., respectively. The chemical structures of ST, the ST-analogous compounds and the structure formula of (±)-1a with the six variable torsional angles are shown in Fig. 1. All other chemicals used were of special reagent grade.

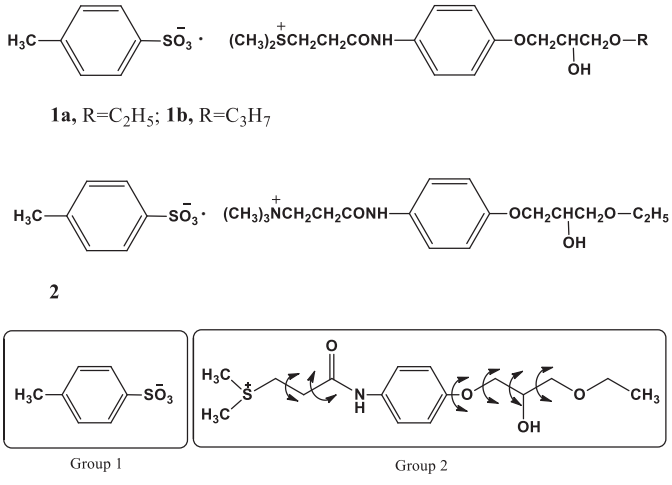

Fig. 1. The chemical structures of suplatast tosilate (1a), the suplatast tosilate analogous compounds (1b and 2), and the structure formula of (±)-1a with the six variable torsional angles.

2.2. Preparation of α-, β-, and δ-form ST crystals

The α-, β-, and δ-forms of ST were prepared following the previously reported procedures (Miura et al., 2003; Tamura et al., 1997; Ushio et al., 1996c).

2.3. Preparation of γ-form ST crystals

Suplatast tosilate (5 g) was dissolved in chloroform (20 mL) and the solvent was evaporated under reduced pressure. Crystals prepared in this way were designated as the γ-form.

2.4. Preparation of ε-form ST crystals

Suplatast tosilate (1 g) was dissolved with heating in 2-propanol (4 mL). After cooling the solution to room temperature, (±)-[2-[4-(3-ethoxy-2-hydroxypropoxy)phenylcarbamoyl]-ethyl]trimethylammonium *p*-toluenesulfonate (2) (approximately 5 mg) was added to act as pseudo-seed crystals. The wet crystals obtained from the solution were added to another solution of ST (5 g) in 2-propanol (20 mL) to act as seed crystals. The crystals that formed were filtered and dried, and classed as the ε-form.

2.5. Preparation of ζ-form ST crystals

Suplatast tosilate (1 g) was dissolved with heating in 2-propanol (4 mL). After cooling the solution to room temperature, (±)-[2-[4-(3-propoxy-2-hydroxypropoxy)phenylcarbamoyl]ethyl]dimethylsulfonium *p*-toluenesulfonate (1b) (approximately 2 mg) was added to act as pseudo-seed crystals. The wet crystals obtained from the solution were added to another solution of ST (5 g) in 2-propanol (20 mL) to act as seed crystals. The crystals that formed were filtered and dried, and classed as the ζ-form.

2.6. Preparation of η-form ST crystals

Suplatast tosilate (5 g) was dissolved with heating in a mixture of acetone (30 mL) and water (0.75 mL). After cooling the solution to 5 °C, the α-form of ST crystals (1a) (approximately 5 mg) was added to act as seed crystals. The crystals that formed were filtered and dried, and classed as the η-form.

2.7. Powder X-ray diffraction measurements

Powder X-ray diffraction patterns of each polymorphic form of ST were determined on a Spectris X'Pert instrument (Spectris Co., Ltd., Tokyo, Japan) with Cu Kα radiation at 40 kV and 30 mA, passed through a nickel filter. The analysis was performed at a continuous scanning rate of 2°/min over a 2θ angular range of 5–35°. The diffractograms obtained were analyzed using Spectris diffraction software.

2.8. Differential scanning calorimetry

Differential scanning calorimetry analysis was performed using a Rigaku 8230 instrument (Rigaku, Tokyo, Japan). A sample (5 mg) was weighed in an open aluminum pan and subjected to a 30–130 °C thermal scan at a heating rate of 4 °C/min with a 100 mL/min dry nitrogen purge.