Polymorphism of a Novel Sodium Ion Channel Blocker

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ABSTRACT: 2-{[4-(4-Fluorophenoxy)phenyl]-methylene}-hydrazinecarboxamide, a member of the semicarbazone family which has shown potential therapeutic use as anticonvulsants, has been found to exist in two polymorphic forms denoted A and B. In addition to reporting aspects of the physical characterization of both forms, the crystal structure of polymorph A has been determined directly from powder X-ray diffraction data using the Genetic Algorithm technique for structure solution, followed by Rietveld refinement. This structure is compared with that of polymorph B, which was determined previously from single crystal X-ray diffraction data. Knowledge of the crystal structures of the two polymorphs provides the opportunity for establishing structure-property relationships. This work further emphasizes the scope and utility of *ab initio* structure solution from powder X-ray diffraction data in the pharmaceuticals field.

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INTRODUCTION

Sodium ion channels have a critical role in the function of the nervous system, where they instigate and conduct nerve impulses by asserting control over the voltage potential across the plasma membrane. Propagation of electrical impulses occurs by opening voltage-gated sodium ion channels. Sodium ion channel blockers prevent this from occurring, and can therefore be used in the treatment of central nervous system disorders and neuropathic pain. A family of aryl semicarbazones[1] has been shown[2] to possess anticonvulsant activity by means of their sodium current inhibiting capacity in nerve cells. In the solid state, these compounds have a tendency to exhibit solvatomorphism,[3] and, as in the case of polymorphism,[4–7] the different crystal forms can exhibit fundamental differences in their physical and chemical properties. From a pharmaceutical standpoint, the different reactivities and stabilities of different crystal forms of a pharmaceutical substance can have a severe impact on the feasibilities of prospective formulations. One particular aryl semicarbazone, 2-{[4-(4-fluorophenoxy) phenyl]-methylene}-hydrazinecarboxamide (Fig. 1; $C_{14}H_{12}FN_3O_2$; 273.26 g mol^{-1}, previously known as Co102862 and here referred to as V102862), has shown promise as an anticonvulsant for the treatment of seizures. As discussed in this report, V102862 has been found to exist in two polymorphic forms. Among the various important issues that stem from polymorphic behavior is the relative bioavailability of formulations in which

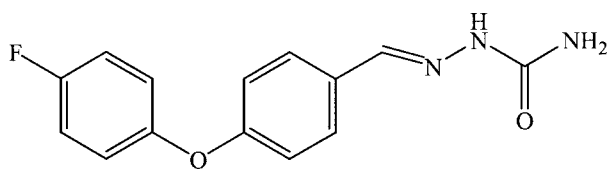

Figure 1. Molecular formula of V102862.

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different polymorphic forms of a drug are utilized; clearly an understanding of polymorphism in any drug system is crucial with regard to its pharmaceutical applications.

The specific aim of the work described herein was to characterize and compare the two crystal forms of V102862, recognizing that knowledge of the crystal structures of the two polymorphs provides the opportunity for exploring and understanding relationships between structure and properties. Importantly, such relationships are a prerequisite for being able to design materials with specific targeted properties. *Inter alia*, this work emphasizes the capability and scope of *ab initio* structure solution directly from powder X-ray diffraction data,[8–10] which has been crucial in establishing the structural properties of one of the polymorphs of V102862.

MATERIALS AND METHODS

General

All solvents and chemicals used in this work were of high-performance liquid chromatography grade. To screen for possible polymorphs, crystallization of V102862 was performed from several solvents. In this work, almost saturated solutions of V102862 were obtained by decanting supernatant and adding a few drops of solvent. Crystallization was performed either by slow evaporation at ambient temperature or by cooling from elevated temperature to ambient temperature at about 1°C/min (see Table 1 in Results). Polarizing optical microscopy was performed using an Olympus Bmax60 Polarized Light Microscope (Olympus America, Melville, NY).

Thermal Analysis

Differential scanning calorimetry (DSC) was performed on a Perkin Elmer Pyris 1 instrument (Sheldon, CT). Sample masses (typically 1–10 mg) were measured accurately (±0.005 mg), with the samples loaded in 50 μL aluminium sample pans crimped with pierced lids. The heating rate for all DSC experiments was 5°C/min, with nitrogen as purge gas (flow rate 30 mL/min).

Vibrational Spectroscopy

Fourier transform infrared spectra (FTIR) were recorded on a Nicolet Nexus 670 spectrometer connected to a Nicolet Continuum FTIR microscope (Thermo Nicolet, Madison, WI) equipped with a 100× objective lens and visible polarization. The samples were ground and prepared as KBr discs (10 mg of V102862 to 20 mg of KBr) for analysis in transmission mode on the FTIR spectrometer. The scan range was 4000 cm^{-1} to 400 cm^{-1} at an instrument resolution of 2 cm^{-1}. For FTIR microscopy, the samples (*ca*. 0.1 mg) were rolled uniformly onto a mirror-coated plate and analyzed in reflectance mode using an MCTA detector from 4000 cm^{-1} to 750 cm^{-1} at an instrument resolution of 2 cm^{-1}.

Dispersive Raman spectra were recorded using a Nicolet Almega Raman spectrometer.

Table 1. Crystallization Conditions Used in the Polymorph Screening Studies

Solvent	Crystallization Method	Solid Phase Produced (Determined by PXRD)
Acetonitrile	Evaporation	B
	Cooling	A
Dichloromethane	Evaporation	B
	Cooling	B
Dimethylformamide	Evaporation	B
	Cooling	B
Ethanol	Evaporation	B
	Cooling	B
Ethanol (95%)/water (5%)	Evaporation	B
	Cooling	B
Methanol	Evaporation	B
	Cooling	B
2-Propanol	Evaporation	B
	Cooling	B

PXRD, powder X-ray diffraction.