Comprehensive Spectroscopic Characterization of Finasteride Polymorphic Forms. Does the Form X Exist?

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Received 7 November 2014; revised 18 December 2014; accepted 5 January 2015

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.24369

ABSTRACT: The pure polymorphic forms I, II, and III of finasteride were prepared and their purity was confirmed by FTIR, differential scanning calorimetry, and X-ray powder diffraction measurements. The preparation experiments demonstrated that the desolvation process of some finasteride solvates does result not only in the formation of polymorphic forms I and II, but also in obtaining the pure form III. The ^{13}C cross-polarization magic angle spinning (CP-MAS) and the ^{15}N CP-MAS spectra can distinguish all three polymorphic forms of finasteride. Additionally, the data point to the presence of only one molecule in crystallographic asymmetric unit of polymorphic forms I and III and two molecules in the form II. The application of electronic circular dichroism (ECD) and vibrational circular dichroism (VCD) spectroscopy for finasteride polymorphic forms shows that the three polymorphs could be distinguished by the characteristic shapes of their VCD spectra in the spectral range 1520–1440 cm^{-1}. The ECD spectral patterns of all these forms, however, are almost indistinguishable because of their close similarity. Comparison of the ^{13}C CP-MAS spectra of forms I, II, and III with those reported in the literature indicates that the so-called finasteride "form X" is identical to the previously known finasteride form III. On this basis, the existence of form X was excluded. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: finasteride; polymorphism; FTIR (Fourier transform infrared spectroscopy); Calorimetry (DSC); solid-state NMR; X-ray powder diffractometry; chirality; circular dichroism

INTRODUCTION

Polymorphic forms of the same substance are characterized by different spatial arrangements and/or occurrences in different conformations. These structural differences are associated with distinct physical properties exhibited by different polymorphs of a compound that, in turn, play a crucial role in the pharmaceutical industry. For this reason, the polymorphic properties of each active pharmaceutical ingredient (API) are studied in detail, and all found polymorphs are fully described.[1,2]

Recently, we have shown that the polymorphic forms of linezolid, which represents APIs, can be successfully distinguished by analysis of their electronic circular dichroism (ECD) and/or vibrational circular dichroism (VCD) spectra.[3] As demonstrated, linezolid represents conformational polymorphism related to its relatively high conformational mobility. What follows is a question whether the application of circular dichroism (CD) as a tool for differentiating polymorphs has a more universal character. In other words, the problem was if CD can also be successfully used in distinguishing polymorphic forms connected to different packing in crystals, that is, packing polymorphs. The finasteride, that is *N*-(1,1-dimethylethyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (Fig. 1), was chosen as a model compound for this study. The selection of finasteride as a model compound was determined by at least two reasons. First, finasteride is a first azasteroid used in the treatment for male pattern hair loss and benign prostatic hypertrophy in modern medicine.[4] In contrast to linezolid, finasteride molecule contains two independent amide chromophores located at opposite ends of rigid steroid skeleton. The principal chromophore, the α,β-unsaturated δ-lactam moiety in ring A, as well as the remaining rings B, C, and D, is practically rigid. The second chromophore, however, being a secondary amide group located at the carbon atom C(17) of ring D, exhibits only a limited rotation around C(17)–C[=O] bond. Thus, finasteride meets the requirements of packing polymorphism and, therefore, gives a second reason for its selection as a model for the present study.

According to the literature, finasteride exists in three or four crystalline polymorphic forms[5–18] and many solvates.[6,8,9,11,12,14,15,19–21] All of these forms have been characterized by the methods chosen from among FTIR, differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), ^{13}C cross-polarization magic angle spinning (CP-MAS) nuclear magnetic resonance (NMR), and single-crystal X-ray diffraction (SCXRD). The polymorphic form I was characterized by FTIR,[5–8,10] DSC,[5,7,10,11,13–15,18] and XRPD[5,10,13,14] techniques. Moreover, the ^{13}C CP-MAS NMR[7,8,11,12] and SCXRD data[6,7] showed that in the crystallographic asymmetric unit only one molecule of finasteride is present.

Abbreviations used: CP-MAS, cross-polarization magic angle spinning; DSC, differential scanning calorimetry; ECD, electronic circular dichroism; NMR, nuclear magnetic resonance; SCXRD, single-crystal X-ray diffraction; VCD, vibrational circular dichroism; XRPD, X-ray powder diffraction.

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This article contains supplementary material available from the authors upon request or via the Internet at http://onlinelibrary.wiley.com/.

Journal of Pharmaceutical Sciences

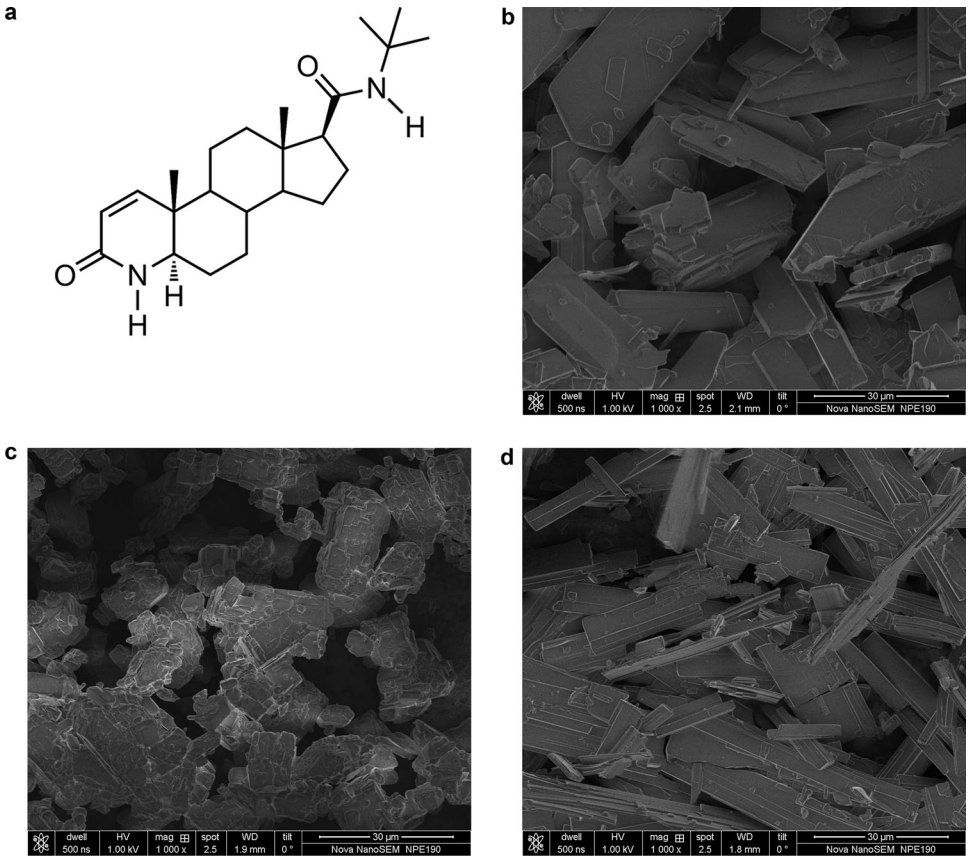

Figure 1. Structure of finasteride (a) and scanning electron micrographs of its polymorphic forms: (b) form I (sample 1), (c) form II (sample 4), and (d) Form III (sample 6).

Polymorphic form II, which can be obtained by the desolvation of finasteride solvates or crystallization of molten finasteride, was characterized by FTIR,[5–8] DSC,[5,7,11] and XRPD[5] methods. In this case, the ^{13}C CP-MAS NMR[7,8,11,12] and SCXRD data[7] unequivocally indicate that the crystallographic asymmetric unit contains two independent molecules of finasteride, thereby distinguishing it from polymorphic form I.

The polymorphic form III, whose preparation was reported only in the patent literature, was identified by FTIR,[9] DSC,[9,13] and XRPD.[9,13] Its crystal structure, however, has not been published so far. Some subsequent attempts to produce form III by the methods described in the original patents failed.[11,12] Instead of pure form III, crystals being the mixtures of different forms, including solvates, were obtained. In one of those mixtures, the presence of form III was suggested on the basis of XRPD measurement.[11,12] In addition, individual signals, most likely corresponding to those of form III, were extracted from the ^{13}C CP-MAS NMR of the same mixture of polymorphs.[11,12] Based on this extraction results, it was suggested that the asymmetric unit of form III contains three independent molecules of finasteride.

Apart from the above, a sample, ostensibly of form I, stored at room temperature for several years, was investigated and described.[11,12] XRPD data indicated that the sample contains some amount of form II together with an unknown polymorph designated by the authors as form X. 2Θ values found in XRPD experiment for form X[11] are very similar to those of form III. The extracted signals in ^{13}C CP-MAS NMR suggested that the form X differs significantly from the form III and that the crystallographic asymmetric unit of form X contains only one molecule of finasteride.[11,12]

A detailed analysis of the above-mentioned literature indicated the necessity to systematize the described data in terms of the number of polymorphic forms of finasteride and their full characterization. Thus, the primary objective of the present work was to organize the existing literature data concerning the number of polymorphic forms of finasteride. Another important task was to verify the existence of form X described by Othman et al.[12] on the basis of complete characterization of all polymorphs of finasteride.

To achieve the intended goal, a number of crystalline samples of finasteride were prepared. They were thoroughly characterized by FTIR, DSC, and XRPD methods and their results were compared with the literature data. The selected samples of pure polymorphic forms of finasteride were additionally analyzed by ^{13}C CP-MAS and ^{15}N CP-MAS. Within the task at hand, particular emphasis was put on the possible application of solid-state ECD and VCD with a focus on determining whether these methods can differentiate all investigated polymorphs.

EXPERIMENTAL

Detailed description of the preparation of finasteride polymorphs as well as procedures for measurements of FTIR, DSC,

 DOI 10.1002/jps.24369