Asian Journal of Chemistry; Vol. 32, No. 8 (2020), 1865-1868

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22665

Identification and Detection of Finasteride Polymorphs in Finasteride Tablets by FT-Raman Spectroscopy

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Received: 7 February 2020; *Accepted*: 31 March 2020; *Published online*: 27 July 2020; AJC-19959

A simple FT-Raman spectroscopic method was developed for identification of finasteride polymorph form in finished dosage form. Finasteride polymorph form I was used in the tablet preparation and the weight fraction of finasteride in tablet was only about 0.023. The method was successfully used to identify the polymorphic form of finasteride in tablet and also to detect up to a level of about 15% of the other polymorph of finasteride present in the solid dosage. The dosage form was characterized by different techniques *i.e.* powdered X-ray diffraction, infrared spectroscopy and Raman spectroscopy. Based on literature survey, only Raman spectroscopy method is able to identify the polymorph of finasteride in dosage form.

Keywords: Identification, FT-Raman spectroscopy, Polymorphs, Finasteride.

INTRODUCTION

Organic compounds of nearly 80-90% in pharmaceutical industry exhibit polymorphism, a property of a material that has to recuperate several crystal structures or forms during crystallization. The identification of the polymorph forms in dosage forms and studying their conversion during manufacture and subsequent storage is essential in recent days for issues related to bioavailability and patents [1]. The polymorphic forms may differ in their physical properties like melting point, heat capacity, solubility and chemical properties like stability [2] and it is very difficult to identify the polymorph form of the drug substance in low dose formulations like the subject formulation. Finasteride (Fig. 1) marketed under the trade name of PROSCAR by Merck & Co. Inc. is 17β-(*n-tert*-butylcarbamyl)-4-aza-5α-androst-1-en-3-one and is 5α-reductase inhibitor for use in treating acne, female hirsutism and particularly benign prostatic hyperplasia. Finasteride exists in two crystalline polymorphic forms *i.e.* form I and form II and different solvated forms [3,4]. The orthorhombic crystal structure of finasteride is referred as form I and monoclinic crystal structure is referred as form II. The form I of finasteride can be transformed

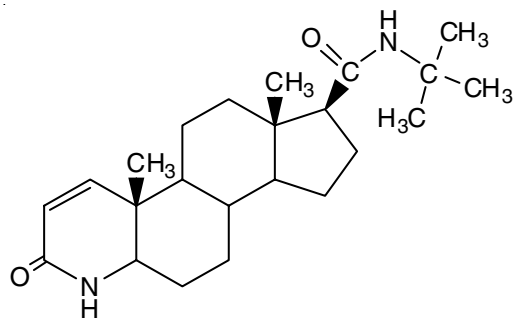

Fig. 1. Structure of finasteride

into form II by heating at 200 to 230 ºC and moreover the identification of the polymorph form in dosage form and polymorph changes during stability is greatly required. The presence of the excipients and low content of finasteride in the tablets about 2.3% by weight makes it difficult to identify the polymorph form of active pharmaceutical ingredient (API).

Generally, for identification of the polymorphic form of drug substance a number of techniques are employed, *i.e.* infrared spectrophotometer (IR) [5], powder X-ray diffraction (XRD) [6-9], synchrotron X-ray powder diffraction [10], differential

scanning calorimetry (DSC) [2], thermal gravimetric analysis (TGA) [8] and solid state nuclear magnetic resonance (SSNMR) [9,11]. The identification of the polymorph form by DSC and TGA is difficult due to the presence of other excipients in the dosage form and also due to the temperature mediated conversion, which can happen in these techniques. The powder XRD is able to identify the polymorph form above l% by weight. The identification of the polymorph form at very low concentration is difficulty by powder XRD technique. Recently, FT-Raman spectroscopy has emerged as a strong tool for identification of the polymorph form of drug substance in the dosage forms [12,13].

The polymorphic forms of finasteride were well characterized by DSC and powder XRD in bulk drugs [7,14]. However in dosage form, the identification of polymorph form of drug substance was difficult by these techniques due to the very low concentration of finasteride in the product. An alternative technique is needed for studying the form conversion of finasteride form during formulation and stability. The aim of this work was to develop Raman spectroscopic method for identification of finasteride polymorph form and detection of polymorph form II present in the pharmaceutical dosage form. This method is simple, less time consuming and moreover the dosage form is directly analyzed without any pretreatment. It also helps to identify the excipients present in dosage form. There are numerous techniques employed to identify the polymorph form in dosage form, however the detection of the very low content of the active pharmaceutical ingredient is very difficult without placebo subtraction. In the present method, no placebo correction is required and the crystalline polymorph form I and form II are free from any extraneous peak from the placebo. The method can be adopted for quantify the content of polymorph form II of finasteride in drug substance as well.

EXPERIMENTAL

Finasteride crystalline polymorph form I and polymorph form II were synthesized in APL Research Centre (A unit of Aurobindo Pharma Limited, Hyderabad, India). Finasteride form II tablet and placebo blend were prepared in APL Research Centre for this study purpose. The PROSCAR, 5 mg tablets (form I) were procured from market.

Sample preparation for Raman spectroscopy

Powders: The sample holder was gold coated and consists of a round shape central cavity and cavity extended to other side of the holder. The holder was kept in such a way that the top face was placed over the stainless steel base. About 30 mg of the sample in the form of powder was poured into the cavity. The sample was gently pressed with the finger press. The sample holder was placed in the mount holds, which holds the sample at the correct height in the sample compartment.

Tablets: The tablet was cut with a razor blade and placed in a spring action clamp holder in the sample compartment.

Raman spectrophotometry: Samples were irradiated with a near infrared Nd: YAG laser operating at 1064 nm in FT-Raman spectrophotometer (Model NXR FT-Raman), Thermoelectron Corporation, USA. The slit aperture was l50 mm and laser power of l.0 W was employed. The CaF_2 crystal as beam splitter with InGaAs detector was used. A 180-degree reflective configuration with fully motorized sample position adjustment was used. A total of 512 scans at resolution of 4 cm^{-1} were acquired for each of standards and samples.

Powder X-ray diffractometry: Samples were exposed to Cu$K\alpha$ radiation (40 kV × 30 mA) in a wide angle powder X-ray diffractometer (Model 3033 TT, Seifert). The Bragg-Brentano focusing geometry was used, with 2º incident aperture slit, a 0.lº detector slit and a scintillation counter as the detector. The instrument was operated in the step-scan mode in increment of 0.03º 2θ and counts were accumulated for 1 s at each step.

Differential scanning calorimetry: DSC thermograms were obtained with Mettler Toledo DSC 821^e system using a heating rate of 20 ºC/min with closed pan under a nitrogen atmosphere with the flow rate of 50 mL/min and sample amount of 2 to 4 mg.

RESULTS AND DISCUSSION

Identification of polymorphs in dosage form by Raman spectroscopic method: The two polymorphic forms were well characterized by XRD and DSC. The XRD pattern matched well with the reported d-values [13,14]. The overlay of powder X-ray diffraction pattern of the polymorphic forms is shown in Fig. 2. The overlay of DSC curves of pure polymorphic forms is shown in Fig. 3. The polymorph form I showed a solid-solid transition at about 233 ºC and finally melted at about 258 ºC. The polymorph form II was melted at about 258 ºC. The DSC values of the two forms were well matched with the reported values [13,14]. FT-Raman analysis was performed as according to previous study [15] for the two polymorph forms of finasteride and Raman spectra are shown in Fig. 4. The Raman shifts between the two forms were clearly distinguishable.

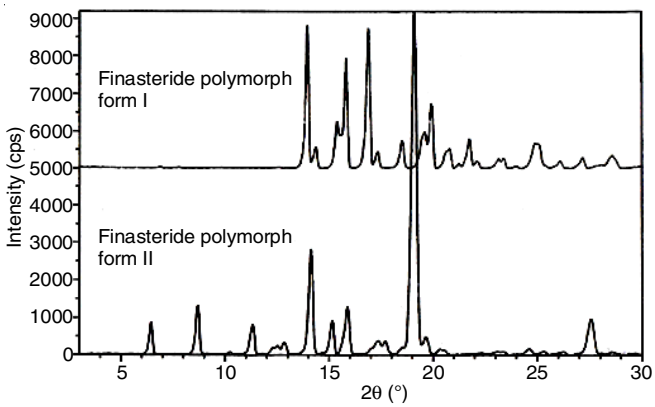

Fig. 2. Overlay of powder diffraction of finasteride polymorph form I and form II

The Raman spectra of finasteride form I and II tablets prepared at APL were recorded. The Raman spectra of the placebo was also recorded. The Raman spectra of form I, form II and placebo are shown in Fig. 5. The two polymorph forms show a clear remarkable difference in the region between l750 and l550 cm^{-1}. No placebo interference was observed in this region and therefore this region is suitable for identification and dete-

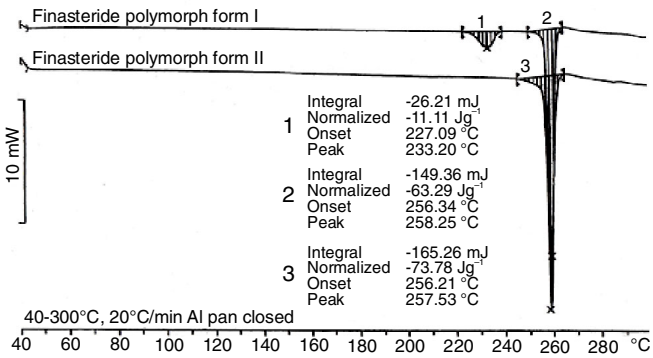

Fig. 3. DSC curves of finasteride polymorph form I and form II

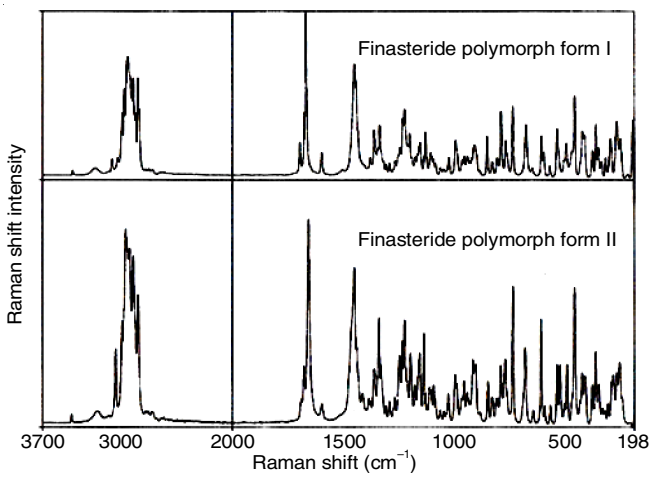

Fig. 4. Raman spectra of finasteride polymorph form I and form II

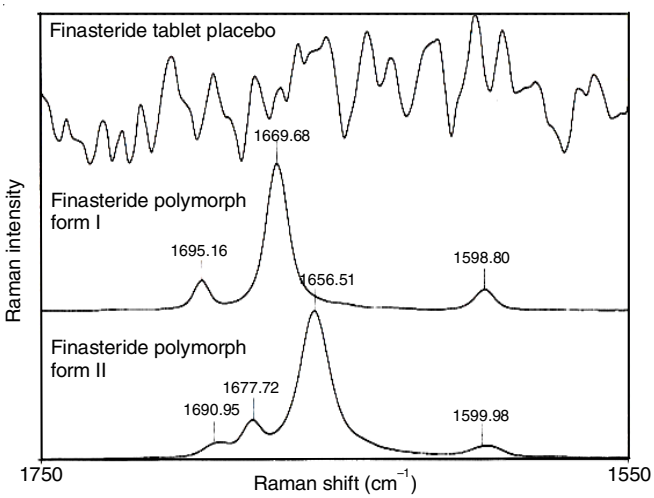

Fig. 5. Raman spectra of finasteride polymorph form I, form II and placebo in the quantification region

ction of the polymorph forms of finasteride in the tablets. The characteristic peaks of the polymorph form I were present at 1670 and l695 cm^{-1}. The characteristic peaks of the polymorph form II were present at about l656 and 1677 cm^{-1}. The peak at l598 cm^{-1} was common for finasteride polymorphic forms.

Detection of polymorph forms in tablet: The Raman spectra of the two polymorph forms clearly indicated that there was no interference from placebo in the region between l750 and l550 cm^{-1}. The major characteristic peak of the polymorph form I was observed at about l670 cm^{-1} and minor at about l695 cm^{-1}. The major peak is used for detection of the polymorph form I in form II tablets. Similarly, the major characteristic peak of polymorphic form II was observed at l656 cm^{-1} and minor peak at l677 cm^{-1}. The major peak of form II was used for detection of the polymorph form II in form I tablets.

The effect of grinding on polymorphic change was evaluated by grinding the pure polymorph forms in mortar and pestle for about l5 min to observe that no polymorph changes occurred during grinding. The powder X-ray diffraction was recorded for grinded samples. The X-ray diffraction pattern of the samples is shown in Fig. 6. The Raman spectrum was also recorded for grinded samples. No polymorph changes were observed in the grinded samples, clearly indicated by Powder X-ray diffraction and Raman spectra of the samples.

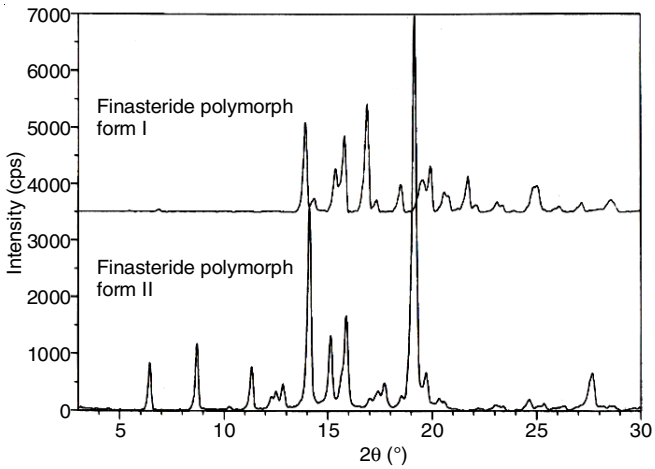

Fig. 6. Overlay of powder diffraction patterns of finasteride polymorph form I and form II grinded for 15 min

A series of mixtures of crystalline polymorph form I in form II of finasteride and *vice-versa* were prepared by geometrical dilution method in the concentration range of 0 to 25% of form I and 0 to 25% of form II by weighing an appropriated amount of form I and form II. Each mixture was grinded in mortar and pestle for about l5 min. These binary mixtures of polymorph forms were separately blended with placebo and weight fraction of finasteride was about 0.023 kept constant.

The two polymorphic forms were overlapped each other due to the less separation of the major peaks. To resolve this problem, a Fourier self-deconvolution (FSD) method was employed for separating the two peaks. The peaks at 1656 and l670 cm^{-1} were separated very well. Detection of the contaminated polymorph form in the tablet was easily feasible. The standard deviation of placebo as a blank in the detection range was determined with l0 measurements. The same parameter of FSD was performed as like sample. Baseline was corrected to minimize the baseline lift and the average noise value was calculated in this region.

The limit of detection (DL) and limit of quantification (QL) were calculated using the following eqns.:

$$DL = s_b \times 3$$

$$QL = s_b \times 10$$

where, s_b is the standard deviation of average blank of each measurement.

Using the above equation, limit of detection was determined and the average minimum height for detection of form II in form I and form I in form II were determined based on the standard deviation of blank. The average minimum height for determining the polymorphic forms was found to be 0.1157 Raman intensity. Any signal above the minimum height at 1670 cm^{-1} for form I and l656 cm^{-1} for form II was able to detect the polymorph forms in the drug products. From the experimental data, it was observed that 15% form I in form II and l5% form II in form I is well above the minimum height require for LOD. The blend was prepared at this predicted level of each polymorph and sampled for six times. The relative standard deviation (RSD) of six determinations of form I in form II was found to be 13.9% and for form II in form I was found to be 24.9%.

The effect of compression on polymorph change was evaluated by compressing polymorph forms of finasteride. It was observed that the compression leads to a change of form II to form I, when a small amount of polymorph form I is contaminated in the drug substance. While a small amount of form II is present in the drug substances, it was observed that there was no conversion of form II. The conversion was absent when grinding was employed. A sample of about 2% form I in form II was prepared and blended with placebo at about 0.023 weight fraction. The blend was compressed at 5 ton and holds for 2 min using a hydrolytic press with the pellet size of l3 mm. This sample was recorded for FT-Raman, the conversion was predominantly to form I. Similarly about 3% of form II in form I was prepared and blended with placebo. This sample blend was compressed at 10 ton and hold for 3 min. No remarkable changes were observed, even though applying a very high pressure. The Raman spectra of compressed blend sample and as such blend of form I in form II samples and form II in form I are shown in Fig. 7. There was no polymorph conversion was observed for pure polymorph forms were treated with high pressure.

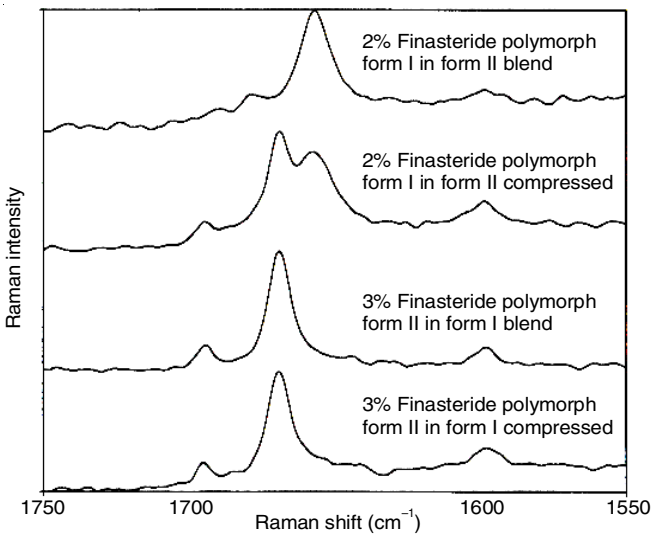

Fig. 7. Raman spectra of compressed blend sample and as such blend of finasteride polymorph of 2% form I in form II sample and 3% form II in form I sample

Conclusion

This study shows that FT-Raman spectroscopic method is useful to detect the very low level of finasteride polymorph form II in polymorph form I even though the drug concentration is less. This method may be employed for routine analysis for observing the polymorph changes during the formulation preparation and drug product.

ACKNOWLEDGEMENTS

The authors are gratefully acknowledge to Aurobindo Pharma Ltd., Research Centre at Hyderabad, India for providing the analytical support to pursue this work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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