FACILE WATER MEDIATED SYNTHESIS OF FINASTERIDE FORM-I, AN AZAANDROSTANE STEROID

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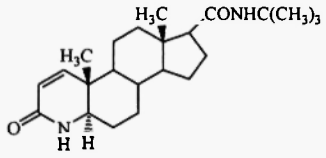
Abstract: A simple and efficient procedure for the selective synthesis of finasteride Form-I from bis-finasteride tetrahydrofuran monohydrate solvate in good yield using ecofriendly solvent water at ambient temperature is established. Powder X-Ray diffraction data (PXRD), and Differential scanning calorimetric (DSC) data of bis-finasteride tetrahydrofuran monohydrate solvate are given.

Introduction

Finasteride is chemically known as 17β-(N-*tert*-butyl carbamoyl)-4-aza-5α-androst-1-ene-3-one. It is a 5α -reductase inhibitor[1], which functions in many androgen-sensitive tissues by converting the major circulating androgenic hormone, testosterone, into the intracellular androgenic metabolite dihydrotestosterone (DHT). Finasteride is used in the treatment of hyper androgenic conditions, such as acne vulgaris, seborrhea, female hirsutism and benign prostate hypertrophy.

Polymorphism can be defined as the ability of the same chemical substance to exist in different crystalline structures. The different structures are referred to as polymorphic, polymorphic modifications or forms[2]. In recent years, there has been considerable interest within industry to find and characterize as many polymorphs as possible of the active molecule of interest, so that the polymorph with the most desirable properties for the targeted application can be selected for development. It is thus essential that, the desired polymorph could be produced reliably and reproducible on large-scale preparation. Polymorphism is a relatively common phenomenon among steroids. Finasteride has been reported[3] to exist in two crystalline non-solvated polymorphic forms designated as finasteride Form -I and Form II. Even though the therapeutic usage of both finasteride Form-I and Form-II were established, finasteride Form-I has been exclusively used in the formulation products.



Finasteride

Other Finasteride polymorphic forms such as Form-III[4], and amorphous form[5] were also reported, however, therapeutic usage of these forms was not established. There are several methods reported for the synthesis of finateride Form-I from the solvents such as ethanol/water[6], acetic acid/water[3], substantially anhydrous solvents[7] selected among n-butyl acetate, isobutyl acetate and by forming complex with group (1) or group (2) metal salts[8]. The polymorphic forms have to be

defined collectively by more than one analytical data such as PXRD, IR, and DSC etc. However, finasteride Form-I, prepared by the reported procedures do not show consistent DSC analytical thermogram. The industrial process for manufacturing finasteride Form-I should yield the reproducible product with consistent polymorphic features. In this communication, we describe a simple and convenient method for the preparation of bis-finasteride tetrahydrofuran monohydrate solvate form and its use for industrial scale production of finasteride Form-I with consistent and reproducible polymorphic features.

Results and Discussions

Finasteride could form unstable pseudo polymorphic form as bis-finasteride monohydrate ethyl acetate solvate form[6]. Similarly it was observed that a stable bis-finasteride tetrahydrofuran monohydrate solvated form was obtained when crude finasteride of having ~ 5% w/w water content was purified with a mixture of ethyl acetate and THF. This tetrahydrofuran monohydrate solvated form was stable at 50-55 °C for several hours. The THF content of this solvated form was estimated to be ~8.5% w/w by ^{1}H-NMR and also water content of ~2% w/w by KF. The solvent contents of this pseudopolymorphic form was further confirmed by thermo gravimetric analysis with a loss of ~11% w/w at ~65 °C which accounts for the sum of ~8.5% w/w of tetrahydofuran and 2% w/w of water. This above data further confirms our assumption that this solvated form is bis-finasteride tetrahydrofuran monohydrate similar to ethyl acetate monohydrate solvated[6] form. The bis-finasteride tetrahydrofuran monohydrate form was characterized by conventional methods of PXRD and DSC. The PXRD diffractogram of tetrahydrofuran solvated form (Figure-1), and IR (Figure-2) was different from the difractograms of other known polymorphic forms. The DSC data showed a minor endotherm with a peak temperature at 109 °C and major endotherm peak at 258 °C (Table-1).

Table -1: DSC and XRD data of the THF solvate and Form-I of finasteride

Compound	DSC Peak temp. (°C)	2θ Values from PXRD data
THF solvate	109, 258	5.44, 6.91, 9.98, 12.12, 14.01, 14.54, 14.73, 15.34, 16.31, 17.57, 18.3, 19.38, 24.40, 29.23, 39.29
Form-I	237, 258	13.9, 14.30, 15.34, 15.77, 16.85, 17.28, 18.48, 19.58, 19.88, 20.74, 21.69, 23.08, 25.04,9 26.05, 28.54, 34.05, 36.47, 37.58, 43.13, 44.20, 47.50

Further it was noticed that even though both ethyl acetate and tetrahydrofuran solvents are available to form solvates during the purification process, finasteride prefers to form thermodynamically stable tetrahydrofuran monohydrate solvate than ethyl acetate solvate. It has been reported[3] that finasteride Form-I could be prepared by crystallization from anhydrous ethyl acetate and finasteride Form-II can be prepared by crystallization from ethyl acetate in the presence of water. So we may assume that crystallization of finasteride in ethyl acetate in the presence of water may yield first a thermodynamically unstable bis-finasteride ethyl acetate monohydrate solvate form, which on further conversion to yield finsteride Form-II instantaneously.

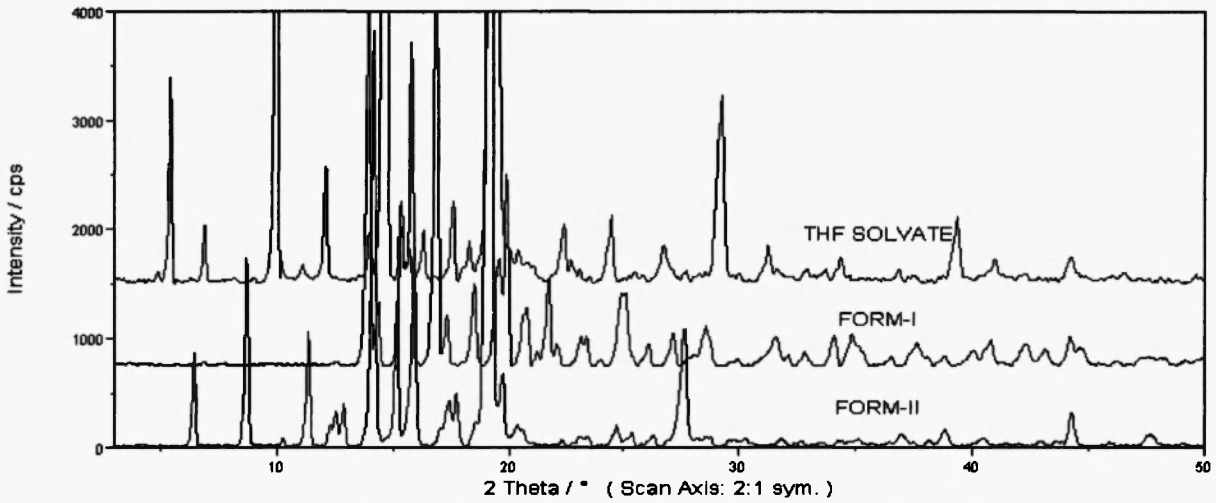


Figure-1: The PXRD of the THF solvate, Form-I and Form-II of finasteride

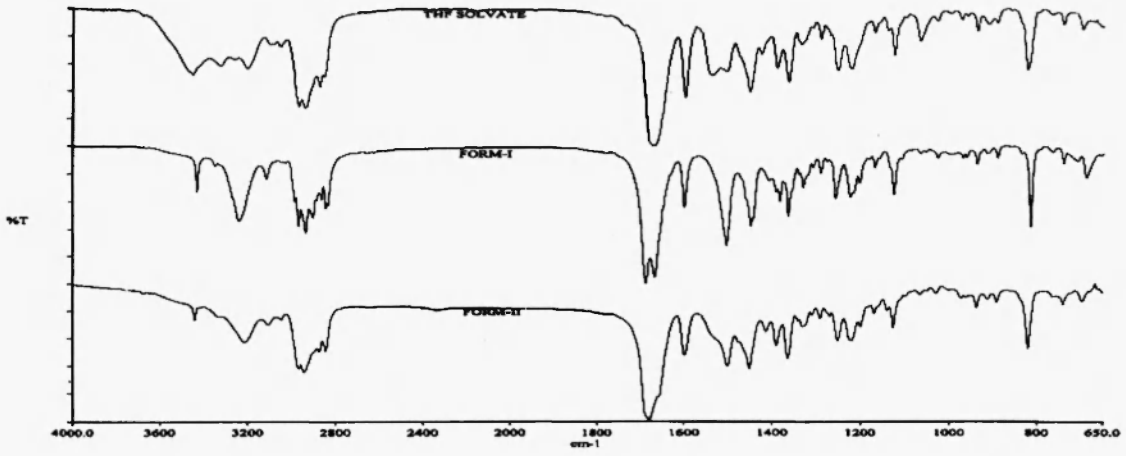


Figure-2: Comparison of IR of THF solvate, Form-I and Form-II.

Since finasteride is yielding thermodynamically stable tetrahydrofuran solvate, it is not further converted to other stable polymorphic forms. However, when tetrahydrofuran solvate was stirred in water at ambient temperature this solvate form converted into finasteride form-I. Finasteride Form-I prepared from tetrahydrofuran solvate form was confirmed by conventional spectroscopic data such as PXRD, DSC and IR and is identical to corresponding analytical data of finasteride Form-I.

In conclusion, the obvious advantages of proposed method are its simple operation, the milder conditions, easy product isolation and prevention of unwanted residual solvents such as acetic acid, ethanol. The present method offers an economical, safe, and environmentally benign alternative to available procedures.

Experimental

The thermal properties of the polymorphs were characterized by conventional method of differential scanning calorimeter using Mettler Model DSC 821^e instrument. The thermograms were recorded under nitrogen atmosphere at a heating rate of 10 °C/min. Powder X-ray diffraction patterns were recorded on a Seifert instrument Model XRD 3003 TT. The X-ray generator was operated at 40 kV and 30mA, using the Kα line of copper at 1.540598Å as a radiation source. It was scanned in the diffraction range of 3° to 50° 2θ at a scan rate of 0.03° 2θ per sec. IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer spectrometer.

17β-(N-*tert*-butyl carbamoyl)-4-aza-5α-androst-1-ene-3-one solvate

Finasteride (150.0g) obtained by the reported method[9] was suspended in mixture of tetrahydrofuran (750 mL) and ethyl acetate (750 mL) was heated to reflux for 1 h. Thereafter, the solution was stirred at 3-5 °C for 2 h. The solid was filtered and washed with ice-cooled mixture of tetrahydrofuran (20 mL) and ethyl acetate (20 mL) and dried at 45-50 °C to get bis-finasteride tetrahydrofuran monohydrate solvate (135 g, 90%). The differential scanning calorimetry (DSC) and PXRD data for THF solvate are given in Table-1.

17β-(N-*tert*-butyl carbamoyl)-4-aza-5α-androst-1-ene-3-one Form-1

Bis-finasteride tetrahydrofuran monohydrate solvate (100.0g) was added portion wise to water (1000 mL) at ambient temperature in 30 min. and was stirred for 4 h. The solid was filtered, washed with water (200mL) and dried at 45-50 °C to get finasteride Form-1 (90 g, 90%). The differential scanning calorimetry (DSC) and PXRD data for Form-I are given in Table-1.

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