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Original Article

Determination of polymorphic forms of finasteride by XRPD, FT-IR, and DSC techniques

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ABSTRACT

The Identification, characterization and quantification of polymorphic forms are becoming increasingly important within the pharmaceutical industry. A variety of different physical analytical techniques is usually necessary for this task. In this work solid-state techniques, Infrared Fourier transform spectroscopy (FT-IR), X-ray powder diffractometry (XRPD) and Differential scanning calorimetry (DSC) were used to analyze polymorphic purity of crystalline Finasteride, an type II 5α-reductase inhibitor. A series of different mixtures of Form I and II were prepared by geometric mixing and their FT-IR spectra, DSC endotherm and XRD patterns were obtained and analyzed, either alone or combined together. A working range of 0–10% (w/w) of crystal Form II in Form I was established with a detection level of 7.5%. The results demonstrate that XRPD may be successfully used to distinguish between the Finasteride polymorphs and to quantify the composition of binary mixtures of the two.

Keywords: Finasteride, Polymorphism, XRPD.

INTRODUCTION

In recent years, polymorphic forms of drugs has attracted a great deal of attention in the pharmaceutical industry, as it is important factor to both bio-availability and formulation characteristics.[1-6] Most pharmaceutical drugs are solids and exist in many different physical forms, such as amorphous or polymorphic crystalline forms. Polymorphism is often characterized as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. It is one of the most important solid state properties of drugs. While polymorphs have the same chemical composition, they differ in their packing and geometrical arrangement, which can affect the pharmaceutically important chemical and physical properties, such as melting point, chemical reactivity, solubility, dissolution rate, powder flow and tableting behaviour. Therefore, different crystalline forms of a pharmaceutically useful compound provide opportunities to improve the performance characteristics of a pharmaceutical product. Accordingly, it is necessary to verify the polymorphism and detect any polymorphic changes in drugs. [7-10] There are a number of techniques for characterizing the solid state properties of pharmaceutical solids, such as optical and electron microscopy, differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA), X-ray analysis, infrared (IR) and Raman spectroscopy. [11-13]

Recently, the Food and Drug Administration (FDA) in US recognized the importance of polymorphs, and required that appropriate analytical procedures be used in drug guidelines to detect polymorphic, hydrated or amorphous forms of a drug. [14-16]

Polymorphic impurity: Organic compounds exists in different solid forms

1. Amorphous forms (disordered)
2. Crystalline forms (ordered)

Polymorphism is the ability of the organic compound to crystallize as more than one different crystal species and polymorphs are different crystalline forms of the same pure compound. [17-18] e.g Polymorphic impurities in Finasteride.

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Finasteride (brand names Proscar and Propecia by Merck, among other generic names) is a synthetic drug for the treatment of benign prostatic hyperplasia (BPH) and male pattern baldness (MPB). It is a type II 5α-reductase inhibitor. 5α-reductase is an enzyme that converts testosterone to dihydrotestosterone (DHT).[19-20]

Finasteride, a 4-azasteroid and analogue of testosterone, works by acting as a potent and specific competitive inhibitor of one of the two subtypes of 5α-reductase, specifically the type II isoenzyme. In other words, it binds to the enzyme and prevents endogenous substrates such as testosterone from being metabolized. 5α-reductase type I and type II are responsible for approximately one-third and two-thirds of systemic DHT production, respectively. [21-24]

EXPERIMENTAL WORKS

The presented work is a compilation of polymorphic impurities identified and quantified in the respective Active Pharmaceutical Ingredients. Two of the polymorphs (Form-I and Form-II) have been described in the patent literature and also in the scientific literature. The other three were only reported in the patent literature novel form II claimed by Reddy in 2005.

Instrumentation

FT-IR: IR was recorded as nujol mull on PE spectrum one. The spectral width was 400cm^{-1}–4000cm^{-1} and the spectral resolution was 2 cm^{-1}. Each spectrum was acquired by performing 32 scans. The spectras of pure Form I, Form II and mixtures of Form II in Form I were obtained..

DSC: DSC was recorded on a Mettler Toledo STAR sytem using 2-4mg of sample in a sealed aluminium crucible without piercing. The Thermograms were recorded between 50^{0}C to 300^{0}C with a heating rate of 20^{0}C/min and using Nitrogen at 50ml/min as purge gas.The thermograms of pure Form I, Form II and mixtures of Form II in Form I were collected.

XRPD: XRPD of the sample are recorded on shimadzu XRD 6000 instrument with a Cu Kα beam. The samples were mounted on 0.2 mm cavity sample holders. A typical continuous scan was performed under the following conditions: Scan type-Standard, Axis- 2θ/θ, Start: 3^0 2θ stop 40^0 2θ at the rate of 2^{0}C/min.The defractograms of pure Form I, Form II and mixtures of Form II in Form I were collected.

Preparation of Finasteride Form-II polymorphism

1. Dissolving finasteride in glacial acetic acid (ca 100mg/ml) and adding water with stirring until the weight % of water equals about75-80%. The resulting solid phase is collected by filtration and dried under vacuum at about 100ºC.
2. Heating form-I up to about 150ºC, holding for a time sufficient to convert form I to form II, for example for about an hour, and cooling back to room temperature.
3. A molten sample of the drug was held at 249 ºC and seeded with a tiny crystal of the form II polymorph. Over a period of several hours, the sample was crystallized in the melting- point capillary.

RESULTS AND DISCUSSION

1. FT-IR spectra of the sample of Finasteride Form-I and Finasteride Form-II were separately recorded under identical condition. Shown in figure 1 & 2. The given FT-IR Spectra is in the region from 4000 cm^{-1} to 400 cm^{-1}.
2. DSC of Finasteride Form-I shows two endotherm onsets at 237.76 and 256.21^{0}C and Form-II shows one endotherm onset at 256.52^{0}C were recorded under identical condition. Shown in fig 3 & 4.
3. XRPD crystalline pattern of the sample of Finasteride Form-I and Finasteride form II separately was recorded under identical condition.Shown in fig 5 & 6. The given XRD pattern is in the region from 3.000 2θ to 40.00^0 2θ.

Different ratio of Finasteride Form II in Form I were prepared

1. A homogeneous mixture of 10% of Finasteride Form II in Finasteride Form I was preapered by mixing it properly. The XRPD crystalline pattern of the sample is recorded under the same conditions as that for Finasteride pure Form I and Form II.
2. The IR spectra and DSC endotherm of the same mixture is recorded under the same conditions as that need to record record Form I and Form II.
3. Similarly a homogeneous mixture of 7.5%, 5% and 2.5% of Finasteride Form II in Form I was prepaired and their XRPD, IR and DSC were recorded in the same manner as above.
4. The data were analysed and a summary of results was prepared as follows

Pure Form I and Form-II show characteristic FTIR, DSC and XRPD patterns. The most distinguishable difference in IR is band at 1677cm^{-1} for Form-II while Form-I shows two well resolved bands at 1688 cm^{-1} and 1688cm^{-1}. The DSC of Form I shows two edotherm a minor one with an onset temperature at about 235ºC while and a major endotherm with an onset temperature at about 254 ºC while Form-II shows only a single endotherm with an onset of 255 ºC. The XRPD cystalline pattern of Form-II shows three distinct diffraction bands at 6.4^{0}2Ɵ, 8.7^{0}2Ɵ and 11.3^0 2Ɵ value which are absent in XRPD of Form-I.

CONCLUSION

The results of the mixtures of 2.5%, 5.0%, 7.5% and 10% of Form II in Form I showed that IR was not able to distinguish even 10% of Form II in Form I from that of pure Form I.

In case of DSC a drift in the onset value of the minor endotherm was observed.

The XRPD was clearly able to show two of the characteristic 2θ values for Form II (8.7^0 and 11.3^0 at 7.5% and 10% of Form II levels in Form I.

Table no.1: Summary of Results

% Form-II in Form I	IR band at 1677	DSC Minor rude onset time	XRPD		
			6.4	8.7	11.3
0	Absent	235^{0}C	Absent	Absent	Absent
2.5	Absent	228ºC	ND	ND	ND
5.0	Absent	226 ºC	ND	ND	ND
7.5	Absent	214 ºC	ND	D	D
10.0	Absent	225 ºC	ND	D	D

Note: ND : Not Distinguishable

D : Distingushable

FT-IR Spectra

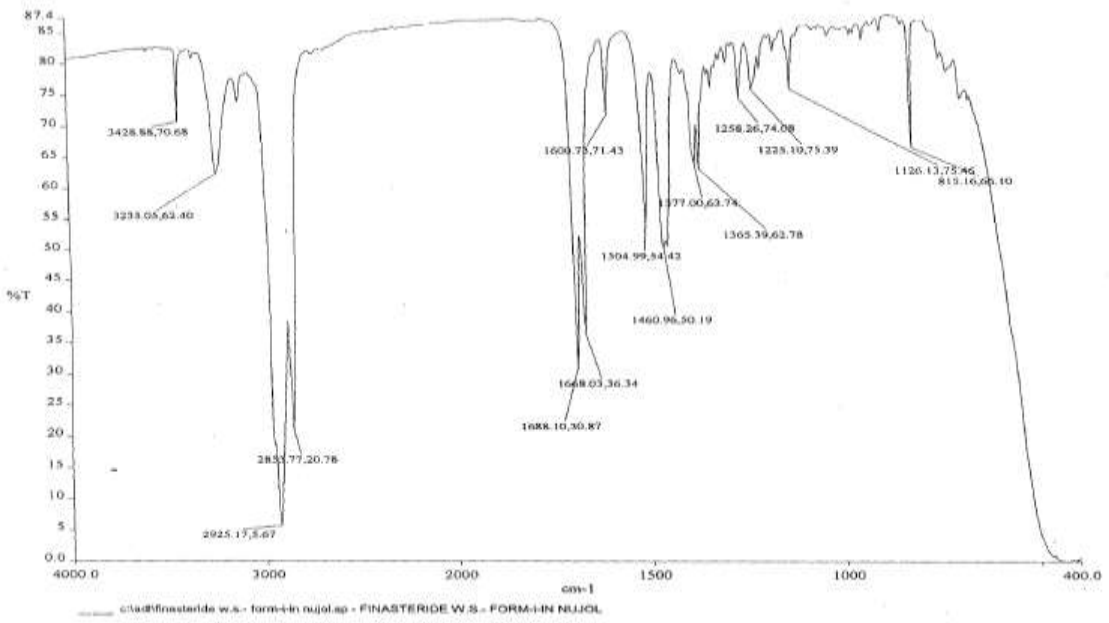

Fig 1: Finasteride Form I Spectra

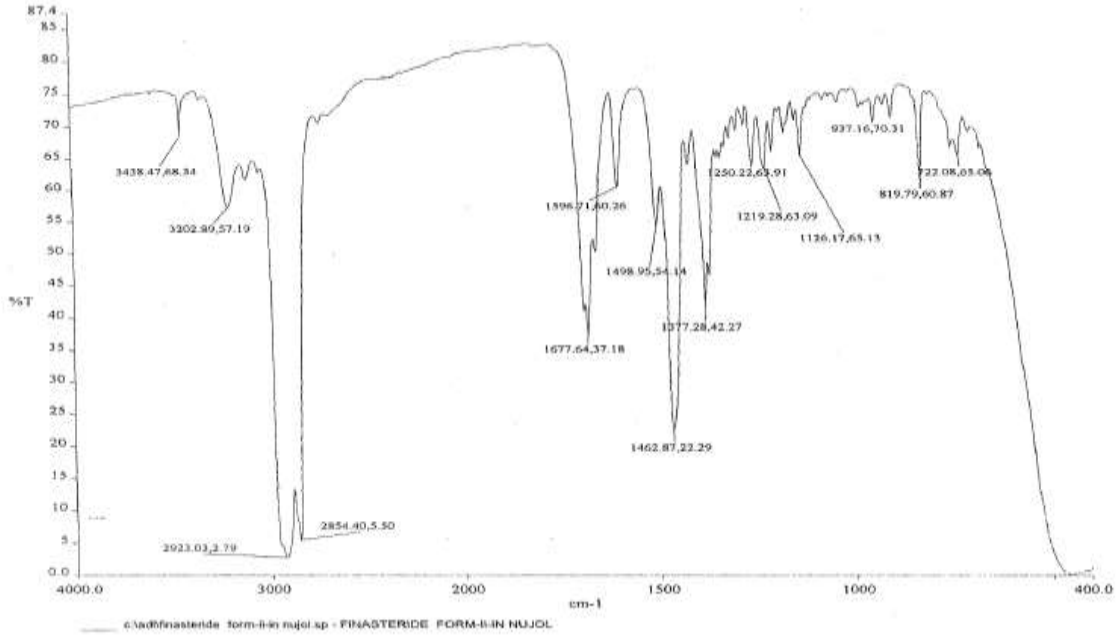

Fig 2: Finasteride Form II Spectra

DSC Thermograms

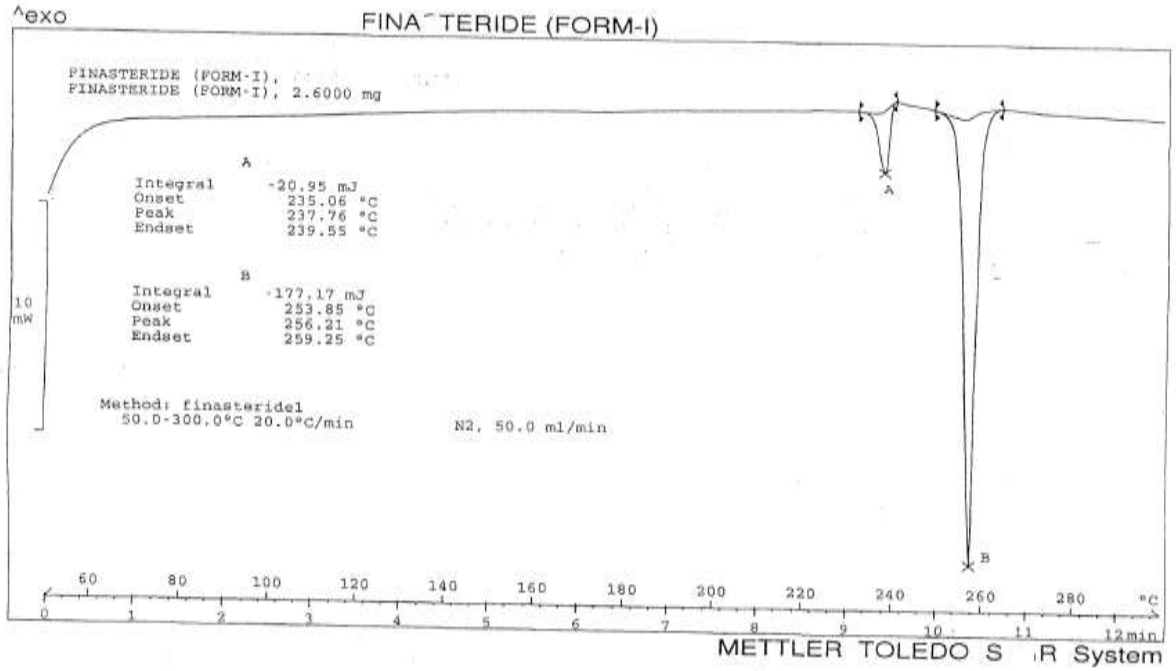

Fig 3: Finasteride Form I Thermograms

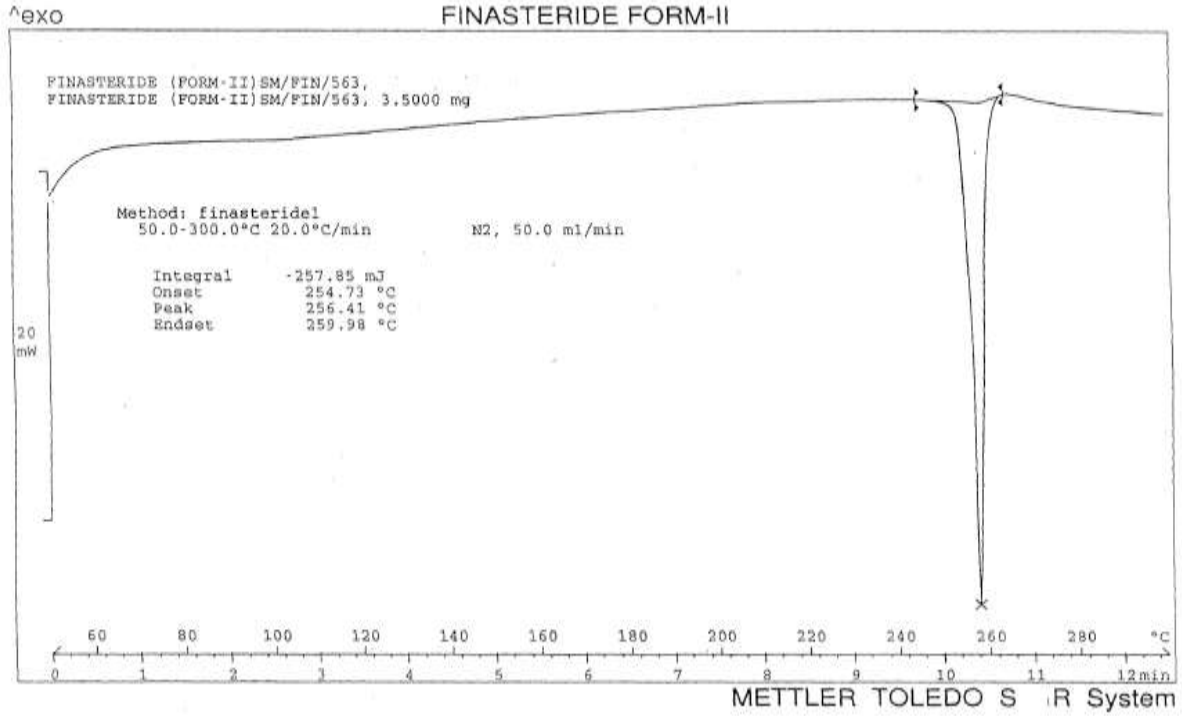

Fig 4: Finasteride Form II Thermograms

XRPD defractograms

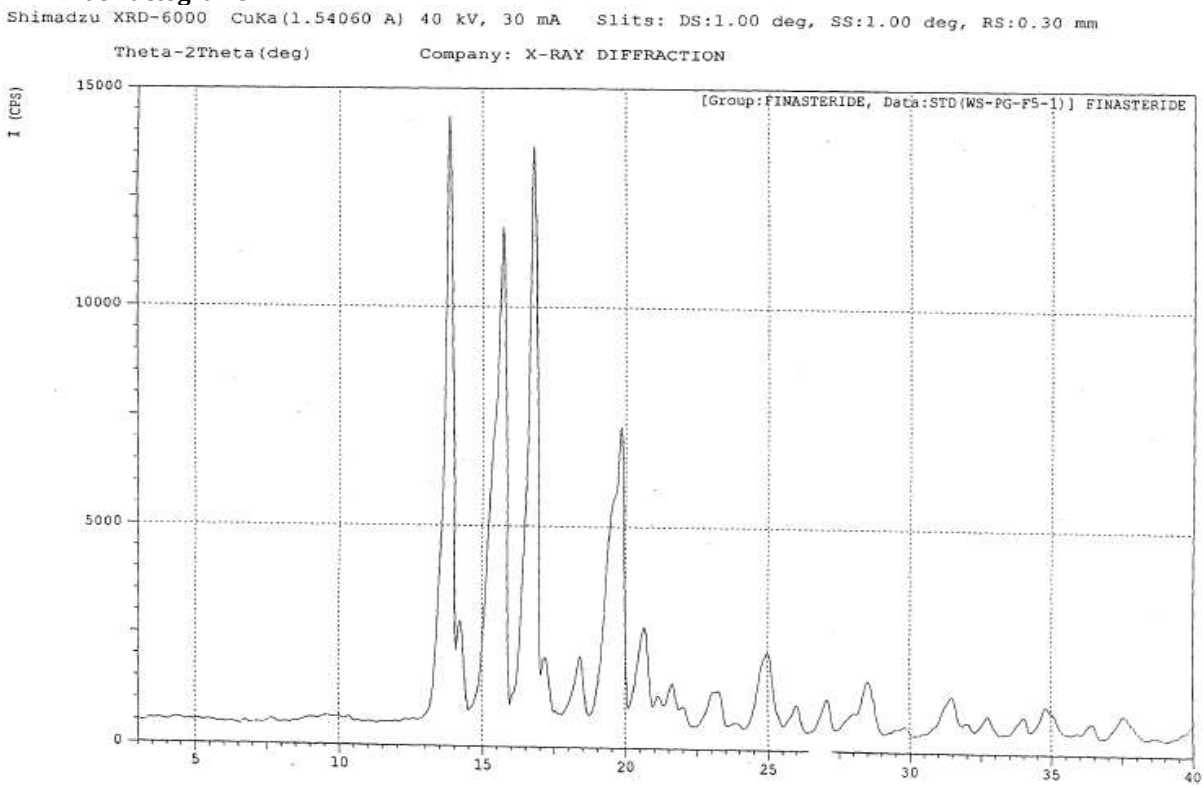

Fig 5: Finasteride Form I Defractograms

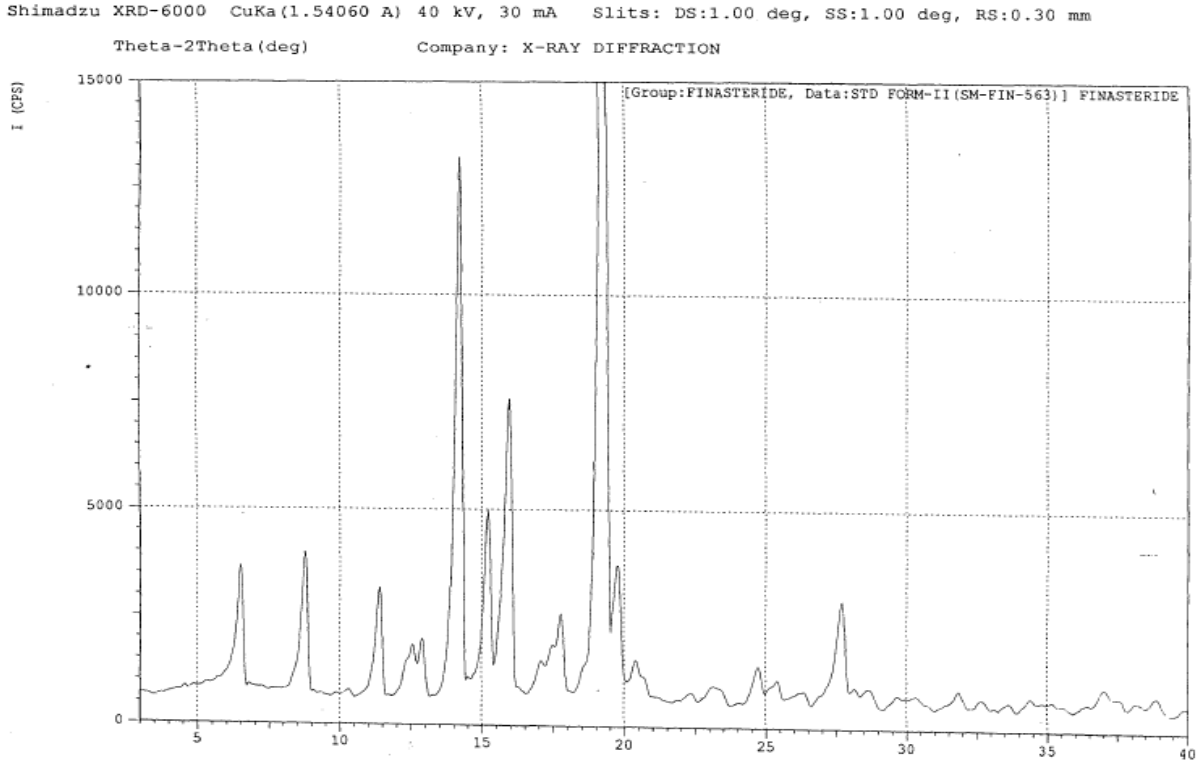

Fig 6: Finasteride Form II Defractogram

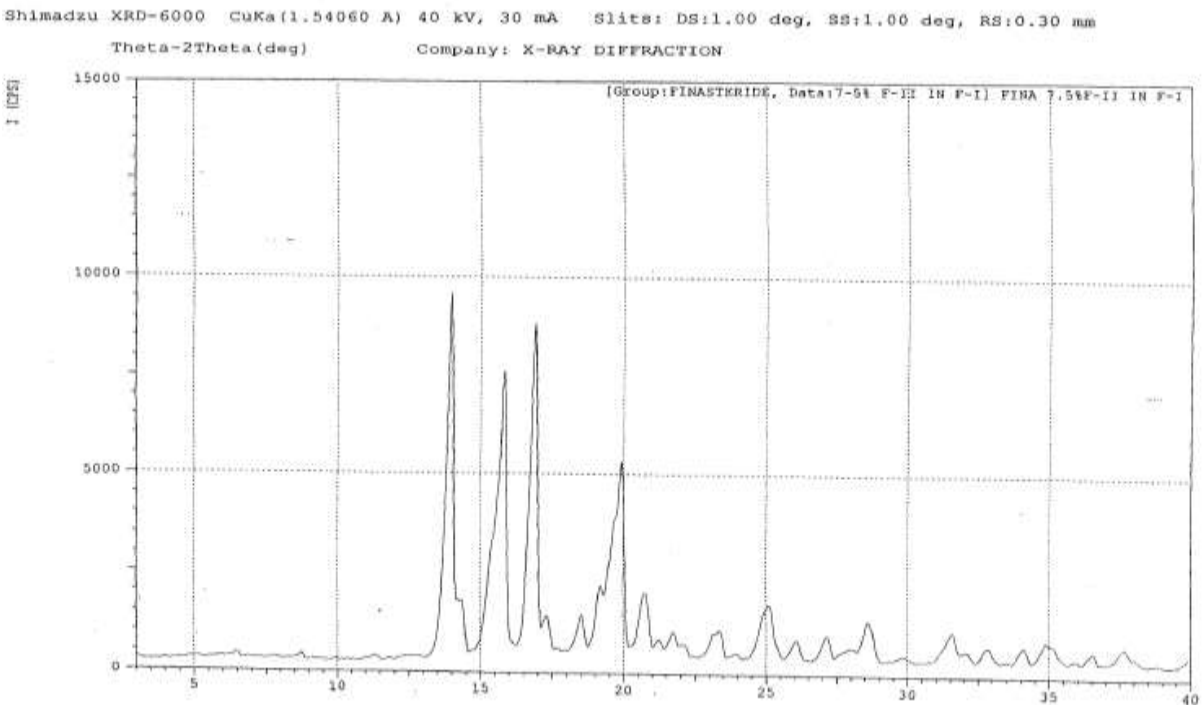

Fig 7: Finasteride 7.5% Form II in Form I.

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