COMMERCIAL SCALEABLE PROCESS FOR THE PREPARATION OF POLYMORPHIC FORM-II OF DUTASTERIDE

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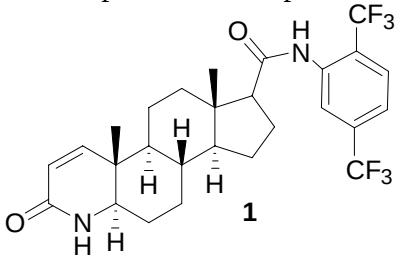
ABSTRACT

*An efficient, simple, consistent and economic process for Form-2 of Dutasteride **1** and characterization by using PXRD and DSC.*

***Keywords**: dutasteride, polymorphism, XRD, DSC*

INTRODUCTION

Dutasteride **1,** is a synthetic 4-azasteride derivative, essentially used for the treatment of prostate diseases such as benign prostatic hyperplasia (BPH), prostate cancer, acne, male pattern baldness and hirsutism.[1,2] Polymorph screening of drug substance is a matter of increasing concern in the pharmaceutical industry. The selection of polymorph is the strategy that is commonly employed to improve physico-chemical properties of active pharmaceutical ingredient.[3-6] During process development of Dutasteride, we encountered two crystalline forms, i.e. form-1 & form-2.[7] The reported process for polymorphic Form-2[8] involves dissolving compound in methanol and co-distillation of methanol with ethyl acetate, followed by isolation of the product with ethyl acetate. This process suffers inconsistency of form-2, if any traces methanol is present in the reaction mass it is affecting to get the required pure form-2 and also results poor yield (73.3%), because the product is highly soluble in methanol, the reported process is not suitable for industrial scale up. Now our aim is to develop a consistent process for form-2 of Dutasteride **1**.



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RESULT AND DISCUSSIONS

Then we thought that saturation method by adopting an anti solvent technique might serve the purpose. The crude Dutasteride **1** dissolving in water miscible solvents such as an alcoholic or

ketonic or acetonitrile. In this way we tried in different alcoholic solvents like methanol, ethanol, isopropanol, *t*-butanol. Ketonic solvents are acetone, methyl ethyl ketone, and acetonitrile (Table 3). Finally we have chosen cost effective methanol as a solvent to dissolve the crude Dutasteride, carbon treatment for decolorization, followed by filtration for particles free, the filtrate was slowly added to water mixture to get the consistent polymorph and good yield (92%).

Table 1: Preparation of Dutasteride Form-2 in water different organic solvents.

S.No.	Solvent	Batch Size (g)	Solvent volume (ml)	Water volume (ml)	Yield (g)	PXRD
1	Methanol	5.0	40	100	4.6	Form 2
2	Ethanol	5.0	70	120	4.2	Form 2
3	Isopropanol	5.0	160	255	4.5	Form 2
4	*t*-butanol	5.0	130	210	4.2	Form 2
5	Acetone	5.0	100	160	4.5	Form 2
6	Methyl ethyl ketone	5.0	125	200	4.0	Form 2
7	Acetonitrile	5.0	510	780	4.3	Form 2

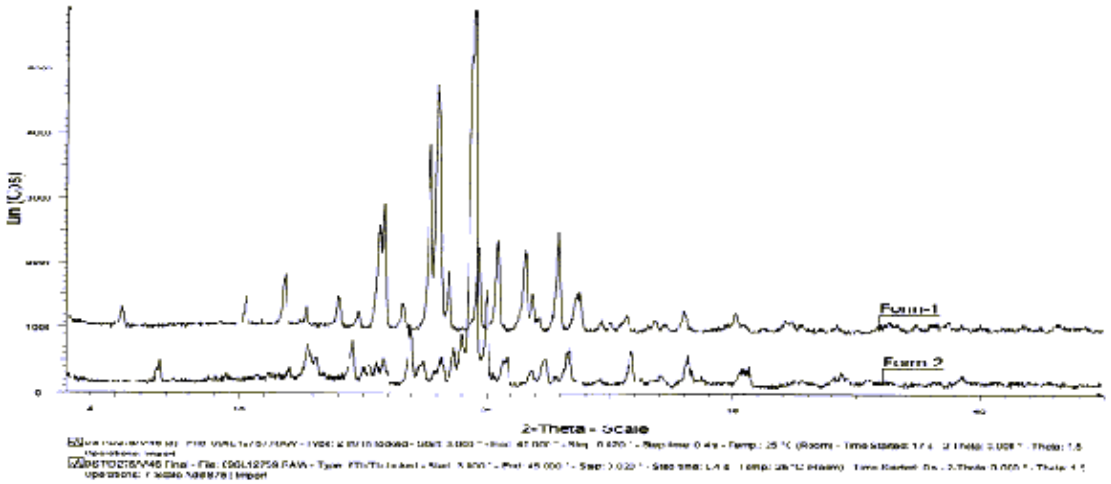

Fig-1: Form1 and Form 2 PXRD of Dutasteride

EXPERIMENTAL

The thermal properties of the polymorphs were characterized by traditional methods of differential scanning calorimeter (Perkin-Elmer. Pyres.6 and Mettler Toledo). The thermo grams were recorded under nitrogen atmosphere at heating rate of 5 ^{0}C/min. Powder X-Ray diffraction patterns were recorded on a D8 ADVANCE BRUKER axs model differentiometer equipped with vertical goniometer in θ/θ (2θ) geometry. Copper Kα (λ= 1.5406 A^0) radiation was used, and the sample was scanned between 3 and 45^0 2θ. The differential scanning calorimetry (DSC) and powder X-Ray diffraction (PXRD) data for these Forms are summarized in the table-2

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Table –2: DSC and PXRD data of the different polymorphic forms of Dutasteride **1**

Form	DSC peak temp. (^{0}C)[a]	2θ values (in deg) from PXRD data
I	251^{0}C↓	16.85, 8.59, 7.44, 6.93, 6.29, 5.95, 5.63,5.58, 5.32, 4.98, 4.89, 4.78, 4.49, 4.32,4.10, 4.04, 3.86, 3.75, 3.59, 3.46, 3.30, 3.17, 2.95, 2.75, 2.65, 2.39 and 2.23
II	258^{0}C↓	13.42, 16.796, 18.575, 6.96, 6.13, 5.27, 4.77, 4.70,4.58, 4.46, 3.82, 6.580, 12.712, 14.445, 18.887, 19.382, 19.907, and 23.258.

[a]↓ denotes endotherm in DSC.

Preparation of crystalline Form-1 of Dutasteride:

Dutasteride crude (5.0 g) was dissolved in dichlomethane (25.0 mL) with stirring. The solvent was partially distilled off (~80%) under reduced pressure. Cyclohexane (50 mL) was added to the resulting residue and the mixture was stirred at 50-60 ^{0}C for 45.0 min. The separated solid was filtered at 50-60 ^{0}C, and washed with cyclohexane (10 mL). The obtained solid dried at 80-90 ^{0}C for 3.0 hr to get the desired crystalline Form-1 of Dutasteride (4.5 g, yield 90%), melting point 251-253 ^{0}C.

Preparation of crystalline Form-2 of Dutasteride:

Dutasteride crude (7.5 Kg) was charged into a clean dry reactor-containing methanol (60 L) and stirred for about 10 min. The reaction mass was heated to 50-52°C to obtain a clear solution. Activated charcoal (0.4 Kg) was charged to the solution and the resulting suspension was stirred for about 15 min. The suspension was filtered through hyflow bed and washed with methanol (15 L). The filtrate was again filtered through a 0.45 micron filter and then was added to a mixture of demineralized water (110 L) and seeding the reaction mixture with pure dutasteride crystalline Form-2 (0.15 Kg) of under stirring, at 25-35 °C for 1-2 hr. The mass was stirred further for about 30 min, the separated solid was filtered and washed with demineralized water (15 L). The solid obtained was dried at 65-70°C under vacuum at 650 mm Hg for 15 hr to yield the title compound (6.9 Kg, yield 92%).

CONCLUSION

We have developed an improved, simple and commercially scaleable process for the Dutasteride polymorphic Form-2, which can provide high throughput and consistent to produce required pure polymorph.

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"If the past cannot teach the present and the father cannot teach the son, then history need not have bothered to go on, and the world has wasted a great deal of time."

-Russell Hoban

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