Crystallization Engineering in Aza-Steroid: Application in the Development of Finasteride

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Supporting Information

1. Purification details
   Page S2
2. Details of recovery of the purified material that was used to pack the column.
   Page S3
3. Analytical techniques experimental details
   Page S3
4. \textsuperscript{1}H-NMR correlation studies
   Page S4
5. Solid state \textsuperscript{13}C-NMR correlation studies
   Page S5
6. IR correlation studies
   Page S6
7. Powder X-Ray Diffraction (PXRD) comparison
   Pages S6-S7
8. Differential Scanning Calorimetry (DSC) comparison
   Page S8
9. Thermo Gravimetric Analysis (TGA) comparison
   Page S9
1. **Purification details**

Complete oxidation of intermediate 2 to afford 1 has not been practically realized. The un-reacted 2 contributes at least 0.5 - 3 % impurity with excellent yield of 1. A further attempt to oxidize un-reacted 2 appears to be impractical since this leads to over oxidation. The isolation of impurity 2 as un-reacted intermediate, in the DDQ and BSTFA oxidation step towards the synthesis of 1, was accomplished by utilizing solid solution formation technique. Such a concept although seemingly implausible was surmised by experiment employing simple filtration of a solution of 1 (containing 1-3% of 2) through a short column of 1 (pad filtration) where 1 essentially acts as a molecular trap and binds the 2 molecules in an irreversible manner; the eluent was essentially free of the impurity 2 (<0.2%) providing deliverable quality of the drug substance.

A slight modification provides same results (Table 1). Instead of using glass column, a saturated solution of impure finasteride (97% pure) was added to a pure finasteride 1 in a round bottom flask equipped with mechanical stirrer. After stirring for 1 h, solid material was filtered. HPLC chromatogram of mother liquor shows 99.8% purity that reflects successful solid solution formation of dihyrdro-impurity on residual finasteride solid. The mother liquor was concentrated to obtain finasteride 1 with 0.2% impurity of 2 in 97% yield, HPLC analysis of residual solid confirms the uptake of impurity 2. HPLC quantification, of impurity 2 in finasteride 1, that was estimated via continuous as well as batch mode protocols are summarized in Table 1.

**Table 1.** HPLC quantification of impurity 2.

<table>
<thead>
<tr>
<th>No.</th>
<th>Dihydro impurity (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Column mode</td>
<td>Batch mode</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial  Final</td>
<td>Initial  Final</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3  0.20</td>
<td>3  0.25</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3  0.21</td>
<td>3  0.27</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3  0.20</td>
<td>3  0.25</td>
<td></td>
</tr>
</tbody>
</table>
2. Details of recovery of the purified material that was used to pack the column.

a) Experiment 1.

10 g of finasteride containing 3% DHF impurity was dissolved in 800 mL of ethyl acetate to prepare saturated solution. This saturated solution obtained above was passed, at a rate of 0.4 mL/min., through the 15 gm of pure finasteride powder (solid) packed in 1.1 cm X 10 cm glass column with 1-2 cm glass beads of 90-150 µ packed from both the end of column.

After completion of elution, either in continuous or batch mode, the impurity level of finasteride drops down to 0.20 to 0.25% from initial 3%. After evaporating the solvent dry powder obtained in 97 % yield (~9.7 g) and the yield of the solid powder recovered from column (continuous mode) or flask (batch mode) was about 102 % (~15.28 g).

b) Experiment 2.

15 g of finasteride containing 3% DHF impurity was dissolved in 1200 mL of ethylacetate to prepare saturated solution. This saturated solution obtained above was passed, at a rate of 0.4 mL/min., through the 10 gm of pure finasteride powder (solid) packed in 1.1 cm X 10 cm glass column with 1-2 cm glass beads of 90-150 µ packed from both the end of column.

After completion of elution, either in continuous or batch mode, the impurity level of finasteride drops down to 0.20 to 0.25% from initial 3%. After evaporating the solvent dry powder was obtained in ~95 % yield (~14.2 g).

3. Analytical techniques experimental details

Polymorphic form-III of finasteride was used in all the experiments. Solvents and regents were used for all the reactions as received. Solid state $^{13}$C-NMR was recorded at 300 MHz. Infrared (IR) spectra were recorded as thin films on a Mattson Galaxy Series FTIR 3000 spectrometer referenced to polystyrene standard. X-ray powder diffraction has been collected on the Rigaku D/Max-2200 model diffractometer equipped with horizontal goniometer in $\theta/2\theta$ geometry. Cu-Kα ($\lambda = 1.5418$ Å) radiation was used and the samples were scanned between 3-45° $2\theta$. Differential Scanning Calorimetric (DSC) analyses were carried out on Shimadzu DSC50. The ThermoGravimetric Analysis (TGA) was performed on Q500 of TA Instruments. The thermogram was recorded from 25 to 250 °C under the nitrogen gas purge at a flow of 40 mL/min for balance and 60 mL/min for sample at a heating rate of 10°C/min. All the experiments were conducted with the solid (either finasteride and dihydrofinasteride are in 1:1 or 1:2 ratio as input).
material obtained from the solution in appropriate solvents like EtOAc or EtOH either by distillation or slow evaporation.

4. $^1$H-NMR correlation studies

$^1$H NMR Correlation

Figure: $^1$H-NMR of (a) Finasteride (b) Dihydrofinasteride (c) 1:1 physical mixture (d) Single crystal of solid solution (which was mounted to record the X-ray).
5. Solid state $^{13}$C-NMR correlation studies
6. IR correlation studies (Finasteride and Dihydrofinasteride have been prepared separately to generate control samples): The indicated value in each panel corresponds to amide –C=O.

![Graph showing IR spectra of Finasteride and Dihydrofinasteride](image)

1: 1 (F:D)
7. Powder X-Ray Diffraction (PXRD) comparison (Finasteride and Dihydrofinasteride have been prepared separately to generate control samples)
Finasteride (1): Dihydrofinasteride (2): 1:1
8. Differential Scanning Calorimetry (DSC) comparison
9. ThermoGravimetric Analysis (TGA) comparison

- Finasteride
- Dihydrofinasteride
- 1:1 (F:D)