Process improvement of atenolol

Nandini R. Pai and *Swapnali Suhas Patil

Department of Chemistry, D. G. Ruparel College, Mahim, Mumbai, Maharashtra, India

ABSTRACT

The aim of this research was to improve manufacturing process of Atenolol resulting into its yield improvement. Atenolol is in a group of drugs called beta-blockers. Beta-blockers affect the heart and blood circulation (blood flow through arteries and veins). Atenolol is used to treat angina (chest pain) and hypertension (high blood pressure). It is also used to treat or prevent heart attack.

Keywords: Atenolol, pressure.

INTRODUCTION

Atenolol slows down the activity of heart by stopping messages sent by some nerves to heart. It does this by blocking tiny areas (called beta-adrenergic receptors) where the messages are received by heart. As a result, heart beats more slowly and with less force. This allows the pressure of blood within your blood vessels to be reduced in case of hypertension (high blood pressure), and helps to prevent abnormally fast heart rhythms, or arrhythmias. As the heart is using less energy, this also helps to reduce chest pain in case of angina. [1]

Atenolol is manufactured in four stages. In the 1st stage, phenol reacts with acetyl chloride in presence of aluminum chloride to give para hydroxy acetophenone; yield of this reaction is 47% of the theoretical yield. In the 2nd stage para hydroxy acetophenone reacts with ammonia in presence of sulphur; yield of this stage is 49.53% of the theoretical yield. So current process is developed by changing physical form of the catalyst, temperature of reaction and moisture content in the reaction which leads to yield improvement of atenolol.

MATERIALS AND METHODS

Purity of the compound was monitored on silica gel 60 F\textsubscript{254} purchased from Merck and solvent from Aldrich chemical Co Ltd. Anhydrous silica gel 60 was used as solid support after dehydration in oven at 100°C for 5 min. Mobile phase used was benzene: ethyl acetate (7:3) as an eluent. TLC spots were detected in UV chamber. Structural interpretation was done by performing Mass spectra, IR and HPLC which were compared with reference standard. [2]

Synthesis of Atenolol

Stage 1 Phenol to Para hydroxy Acetophenone

32g (0.284 mol) of MCB was charged in the reactor; to it 38 g (0.28 mol) of aluminum chloride flakes were gradually added at RT and reaction mass was stirred for 30 min. Chilled reaction mass to 10°C. Gradually added mixture of (15g phenol (0.159 mol) +8g MCB (0.071)) below 15°C. Chilled reaction mass to 5°C and added 13.5 g (0.172mol) of acetyl chloride and reaction mass was maintained for 2 h at 5 to 10°C. Completion of reaction was monitored on TLC. Quenched reaction mass in mixture of ice and hydrochloric acid (120 g of ice + 10 g of HCl
Pelagia Research Library

(0.274 mol)). Stirred for 30 min and filtered to obtain solid. Dried to get 10.20 g (0.075 mol) i.e. 47% of theoretical yield of para hydroxy acetophenone.

Stage II: Para hydroxy acetophenone to para hydroxy phenyl acetamide
1453 g (24.21 mol) of isopropyl alcohol (moisture below 0.5%) was charged in SS autoclave; to it 500 g (3.311 mol) of para hydroxy acetophenone and 150 g (4.687 mol) of sulphur (roll) were added under stirring at RT. 150 g (8.823 mol) of ammonia was purged and reaction mass was gradually heated to 160 to 165°C i.e. 30-35 kg/cm² pressure. Reaction was maintained for 10 hrs. Cooled to 70°C i.e. pressure 3 to 5 kg/cm² and transferred to SS reactor. Concentrated IPA atmospherically upto 70% of its total volume. Cooled RM to RT, filtered to get 360 g of crude PHPA. [3][4]

360 g of crude PHPA was charged in reactor; to it 3600 mL of water was added and heated to 90-95°C, stirred for 30 min and checked for complete dissolution. 12.5 g of charcoal and 24.43 g of sodium hydro sulphide (hydrous) are then added and stirred for 30 min. Then the reaction mass was filtered through sparkler filter. Clear filtrate was cooled to room temperature and then chilled to 0-5°C. The solid was filtered and dried to get 275 g (1.821 mol) of PHPA i.e. 49.53% of the theoretical yield.[5]

Improved Process
Stage I
By changing some physical parameters in the industrial process such as size of aluminium chloride i.e. particle size, reaction was scanned for the range given below and found to be responding for yield improvement (refer Table 1). Second parameter was temperature which was changed while addition of acetyl chloride and maintaining temperature which also gave yield improvement.[5]

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Mesh size of aluminium chloride</th>
<th>% yield compared with theoretical yield.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initial aluminium chloride flakes 20 micron and above</td>
<td>47%</td>
</tr>
<tr>
<td>2</td>
<td>9-20 micron</td>
<td>58%</td>
</tr>
<tr>
<td>3</td>
<td>2-9 micron</td>
<td>72%</td>
</tr>
<tr>
<td>4</td>
<td>Below 2 micron</td>
<td>73%</td>
</tr>
</tbody>
</table>

Table 2 Temperature of reaction mass while addition and maintained

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Temperature in °C</th>
<th>% yield compared with theoretical yield.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initial 5°C - 10°C</td>
<td>47%</td>
</tr>
<tr>
<td>2</td>
<td>0°C - 5°C</td>
<td>53%</td>
</tr>
<tr>
<td>3</td>
<td>-5°C to 0°C</td>
<td>69.21%</td>
</tr>
<tr>
<td>4</td>
<td>-10°C to -5°C</td>
<td>70%</td>
</tr>
</tbody>
</table>

When both the parameters were combined, there was maximum yield improvement. So the improved process was carried out as follows:

32 g of MCB was charged into the reactor; to it 38 g of AlCl₃ powder was added (mesh size 2-9 micron), stirred reaction mass for 30 min. Chilled reaction mass to 10°C and then the mixture of phenol and MCB (15g in 8 g) was added below 15°C. Reaction mass was further stirred for 30 min and chilled to -5 to 0°C. Gradually 13.5 g of acetyl chloride was added and reaction mass was maintained at -5 to 0°C for 2 h. Completion of reaction was checked on TLC and then reaction mass was quenched in mixture of 120 g of ice and 10 g HCl. Further reaction mass was stirred for 30 min and solid obtained was filtered and dried to get 16.5 g of PHAP.[7]

Stage II
In this stage particle size of sulphur was changed (decreased) to provide more surface area. Reaction was carried out in powder form and found to give yield improvement Table 3. Second parameter was moisture content in the reaction mass which was increased to give better yield (Table 4).

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Sulphur</th>
<th>% yield compared with theoretical yield.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initial sulphur roll</td>
<td>49.53%</td>
</tr>
<tr>
<td>2</td>
<td>Sulphur Powder</td>
<td>59.23%</td>
</tr>
</tbody>
</table>
Charged 1453 g of IPA containing 10% moisture in SS autoclave; to it added 500 g of PHAP and 150 g of sulphur powder at RT under stirring. Purged 150 g of ammonia at RT and reaction mass was gradually heated to 160 - 165°C i.e. 30 to 35 kg/cm² pressure which is maintained for 10 h. Cooled RM to 70°C i.e. 3 to 5 kg/cm² pressure Transferred to SS reactor. Concentrated IPA atmospherically to its 70% of total volume Cooled RM to RT and then centrifuged to get 490 g of crude PHPA.

In SS reactor 490 g of PHPA was charged and 4900 mL of water was added and heated to 90 - 95°C. Checked for complete dissolution and then added 33.26 g of hydrous and 16.5 g of charcoal with stirring for 30 min at 90-95°C. Then it was filtered hot through sparkler filter to collect clear filtrate in SS reactor which was cooled to RT and then chilled to 0-5°C. The solid obtained was filtered and dried to get 360 g (2.384 mol) of pure PHPA i.e. 64.84% of theoretical yield.

Calculation of yield
According to yield Theoretical yield can be calculated

Stage I
94 g Phenol ————> 136 gm PHAP (Theoretical calculation)
Ideal reaction 15 g of phenol gives ————> 21.70 g of PHAP =100%
Industrial process 15 g of phenol gives ————> 10.20 g of PHAP = 47% of theoretical yield
Improved process 15 g of phenol gives ————> 16.5 g of PHAP = 76% of theoretical yield
Stage II
136 g of PHAP ---------------------151 g of PHPA (Theoretical calculation)
Ideal reaction theoretical output 500 g of PHAP -------------------55.147 g of PHPA 100%
Industrial process 500 g of PHAP---------275 g of PHPA 49.53 % of theoretical yield.
Improved process 500 g of PHAP ---------360 g of PHPA 64.84% of theoretical yield.

CONCLUSION

In stage I, yield increase is by increasing surface area of AlCl₃, i.e. powder form and addition of acetyl chloride is done at -5 to 0°C instead of 5 to 1 °C as ortho substitution decreases which leads to increase in yield.

Stage II, yield increase is by increasing surface area of sulphur and by increasing moisture content in the reaction as the moisture helps in the solubility of ammonia gas.

Acknowledgements
I am thankful to Ultratech India Ltd. and D. G. Ruparel College for providing all the necessary analytical details of the compound, required support and co-operation for executing this project. I am also thankful to Mr. Deepak U. Shanbhag for help and cooperation.

REFERENCES

[4] Name reaction by Li Jie Jack