An Improved Commercially Feasible Process for Flecainide Acetate

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Commercially viable manufacturing process for Flecainide Acetate (I) conforming to regulatory specification and cost effective process is reported. Specifically, an improved process for the preparation of Flecainide Acetate allows isolation of anhydrous hydrochloride salt of Compound III, which facilitates the reduction of the pyridine ring with the only catalytic amount of platinum on carbon within 2 hours Therefore, simplifies the synthesis and isolation of Flecainide acetate on a commercial scale to a considerable extent.

Keywords: Cardiac depressant; catalytic hydrogenation; platinum catalyst; antiarrhythmic; boric acid.
1. INTRODUCTION

Flecainide acetate, chemically known as N-(2-piperidinylmethyl)-2,5-bis(2,2,2-trifluoroethoxy) benzamide acetate and represented by Formula I is an antiarrhythmic agent also known as cardiac dysrhythmia medication. Antiarrhythmic agent used for the prevention of abnormal fast rhythms of the heart. Flecainide acetate works by blocking the sodium channel in the heart, slowing the upstroke of the cardiac action potential. This thereby slows conduction of the electrical impulse within the heart. Other medication includes in this class are encainide, propafenone and moricizine.

Various researchers have attempted to synthesize pharmaceutically acceptable Flecainide Acetate of formula I. However, these methods are tedious, poor selectivity of pyridine ring reduction, lower yield, high loading of catalyst, longer reaction time result in a higher cost of the final API and additional purification render these process unviable on commercial scale [1-3]. Hydrogenation is the second step in synthetic route, it is very important for the efficient synthesis of compound II particularly for the minimization of reaction time with less loading of catalyst and unwanted side product at commercial level. Though numerous methods of Flecainide acetate are reported, an improved process with detailed impurity profiling is not yet reported.

From the literature, it was evident that there is a need for improvement in the manufacturing process of Flecainide acetate in terms of selectivity, specifically for the reduction of the pyridine ring of compound III, cost effectiveness, controls the formation of impurities below regulatory limits and which does not require column chromatography or repeated crystallization for getting the desired purity at commercial scale.

2. EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by the manufacturers. Varian $^1$HNMR spectra (400 MHz) and $^{13}$CNMR spectra (100 MHz) instrument were recorded in DMSO-d$_6$, and mass spectra were determined on the API-2000LCMS mass spectrometer, Applied Biosciences. IR spectrum was taken in potassium bromide and recorded on Shimadzu 8400S FTIR instrument. Differential scanning calorimetry (DSC) analysis was carried on Perkin Elmer DSC8000 instrument.

Fig. 1. Flecainide Acetate (I)

Fig. 2. Compound- III
Example 1: Preparation of 2, 5-Bis (2, 2, 2-trifluoroethoxy)-N-(2-pyridylmethyl) benzamide Hydrochloride (Compound- III)

2, 5-Bis (2, 2, 2-trifluoroethoxy) benzonic acid (75 kg, 1.0mol), 2-aminoethyl pyridine (34.4kg, 1.35mol), boric acid (0.145 kg, 0.1mol) and toluene (450L) were added to a flask and heated at 110 to 115°C and water was removed by azeotrope over 12 hours. After monitoring reaction progress by HPLC toluene was distilled off under vacuum, water (150L) was added and stirred for 2 hours at 25 to 30°C. Precipitated solid was filtered and washed with water (150L), dried under vacuum for 4 hours to give free base of 2, 5-Bis (2, 2, 2-trifluoroethoxy)-N-(2-pyridylmethyl) benzamide. Ethyl acetate in (225L) and 75kg 2, 5-Bis (2, 2, 2-trifluoroethoxy)-N-(2-pyridylmethyl) benzamide were added to a flask and added cooled 10% solution of ethyl acetate in HCl (150L) were added to clear solution. Filtered the precipitated hydrochloride salt of title compound (III) as a white solid after drying under vacuum below 70°C (90 kg, 99.91% purity) in 85.8% yield.

1H NMR (DMSO-d6) δ: 4.75-4.87 (m, 6H), 7.21-7.28 (m, 2H), 7.34 (d, 1H), 7.83-7.88 (m, 2H), 8.40 (t, 1H), 8.80 (d, 1H), 9.06 (t, 1H). 13C NMR (DMSO-d6): δ161.61, 154.24, 149.35, 145.59, 141.48, 128.11, 116.09, 66.76, 64.84, 40.69, 138.87. ESI-Mass for C17H16F6N2O3Cl: 409.2. C NMR as Sodium adduct (M+H)+. IR: 3350, 3136, 3069, 2218, 1632, 1593, 15551115 cm⁻¹. Elemental analysis: Calculated: C (48.11 %), H (4.97 %), N (6.12 %) Found.

Example 2: Preparation of Benzamide, N-(2-piperidinylmethyl)-2, 5-bis (2, 2, 2-trifluoroethoxy) (Compound - II)

2, 5-Bis (2, 2, 2-trifluoroethoxy)-N-(2-pyridylmethyl) benzamide Hydrochloride (90kg, 1mol), 1.8kg Platinum on carbon (50% wet) and methanol (90L) were taken in pressure reactor and heated to 60-65°C for 4hr at a hydrogen pressure of 12kg/cm². After monitoring reaction progress by HPLC, the mixture was cooled to 25-30°C and filtered the catalyst. The filtrate was added into a solution of sodium carbonate (90kg) and Water (90L) and Precipitated solid was filtered and dried under vacuum to give title compound II (75kg, 99.78% purity) in 89.4% yield.

1H NMR (DMSO-d6) δ: 0.96-1.48 (m, 4H), 1.58-1.72 (m, 2H), 1.93 (brs, 1H), 2.44-2.92 (m, 3H), 3.11-3.23 (m, 2H), 4.72-4.82 (m, 4H), 7.16-7.21 (m, 2H), 7.27 (d, 1H), 8.03 (t, 1H). 13C NMR (DMSO-d6): δ 164.39, 151.87, 149.20, 128.10, 115.69, 66.65, 55.72, 46.19, 45.15, 40.12, 30.87, 24. ESI-Mass: For C15H20F6N2O3. 415.1((M+H)+). IR: 3302, 3136, 3069, 2218, 1632, 1593, 15551115 cm⁻¹. Elemental analysis: Calculated: C (43.43 %), H (4.82 %), N (6.75 %), Obtained: C (45.73 %), H (4.97 %), N (6.12 %) Found.

Example 3: Preparation of Flecainide Acetate (I)

Benzamide, N-(2-piperidinylmethyl)-2, 5-bis (2, 2, 2-trifluoroethoxy) (75kg, 1mol) and methanol (450 L) were added to a flask and heated at 55 to 65°C to get clear solution. Added acetic acid (16.2kg, 1.5mol) to clear solution at 55 to 65°C and stirred for 1 hour. After distillation of methanol under vacuum charged Isopropyl alcohol (300 L) into reaction mass and cooled at 25-30°C. After stirring for 2 hours filtered the precipitated pure Flecainide acetate and drying under vacuum below 70°C for 8 hours gives title compound I (78kg, 99.88% purity) in 90.8% yield.

1H NMR (DMSO-d6) δ: 1.01-1.51 (m, 4H), 1.61-1.73 (m, 2H), 1.87 (s, 3H), 2.46-2.64 (m, 2H), 2.93-2.96 (m, 1H), 3.14-3.26 (m, 2H), 4.18 (brs, 1H), 4.72-4.81 (m, 4H), 7.16-7.21 (m, 2H), 7.27 (d, 1H), 8.11 (t, 1H). 13C NMR (DMSO-d6): δ22.71, 23.05, 24.08, 28.16, 43.39, 44.91, 55.38, 64.83, 66.83, 115.97, 116.23, 117.68, 119.71, 125.25, 128.14, 149.26, 151.89, 164.93, 173. ESI-Mass: For C17H20F6N2O3. 415.0((M+H)+). IR: 3404, 2938, 1647, 1541, 1288, 1084 cm⁻¹. Elemental analysis: Calculated: C (48.11 %), H (5.10 %), N (5.90 %), Obtained C (48.42 %), H (5.13 %), N (5.85 %) Found. DSC: peak observed at 151.53.

3. RESULTS AND DISCUSSION

An improved process which is free from impurities associated with existing synthetic routes and does not utilize column chromatography or other tedious purification methods and is highly selective towards reduction of the pyridine ring with low loading of catalyst with less reaction time is described.

The optimization of catalytic hydrogenations is often a challenging problem due to the difficulty in predicting the changes that will occur from even minor variations in experimental conditions [4]. However, a systematic approach can lead to significant improvements in important processes.
Flecainide Acetate consists of two trifluoroethoxy group which show sensitivity towards reduction. Reactions particularly with high loadings of catalyst, longer reaction time, high hydrogen pressure and higher temperature lead to removal of trifluoroethoxy group ended with trans-etherification product [5,6] and other unwanted impurity. In order to avoid loss of trifluoroethoxy group, we focused on reduction of compound III, to reduce reaction time and catalyst with low loading.

If hydrogenation was stopped early, too much starting material left unreached, it was difficult to restart the hydrogenation due to catalyst deactivation. On the other hand, loss of trifluoroethoxy group could be suppressed by reducing the contact time of the product with solvent and catalyst.

By keeping these aspects in mind, the catalytic hydrogenation of II was investigated with a wide selection of catalysts, and the results are tabulated in Table 1. Reactions with several other catalysts (PtO2, Rh/C, Ra-Ni, Ru/C, and Pd/C) were attempted and it was observed that, even after 30% loading of catalyst under 15-20 kg/cm² hydrogen pressure rendered the reaction incomplete after a prolonged period of times, which leads to poisoning of catalyst initiating the formation of undesired product [7,8]. Reduction reaction was monitored by TLC and found that the reaction was contaminated with unknown impurity and it was very difficult to remove this impurity once it formed. The resulting impurity was identified and the structure was confirmed by 1H NMR and mass spectrometry as Dimethoxy impurity, this could be formed by loss of the trifluoroethoxy group (trans etherification product A) in presence of methanol at high temperature, high pressure with high loading of catalyst.

![Fig. 3. Dimethoxy impurity](image)

**Table 1. Catalytic hydrogenation of Compound III**

| Entry | Catalyst | Results* | Reference |
|-------|----------|----------|-----------|
| 01.   | 10 % Pd/C, 50 % wet | Incomplete reaction after 20 hours with impurity formation, catalyst poisoning | 7,14 |
| 02.   | 20 % Pd/C, 50 % wet | Incomplete reaction even after 15 hours with impurity formation, catalyst poisoning | 5,7 |
| 03.   | Raney Ni/C, 50 % wet | Incomplete reaction after 24 hours, catalyst poisoning | 4 |
| 04.   | Rh / C, 50 % wet | Incomplete reaction after 15 hours with impurity formation, catalyst poisoning | 6,7,8 |
| 05.   | 10 % Pd/C, 50 % wet, aq. HCl | Incomplete reaction after 24 hours, high loading of catalyst with impurity formation, catalyst poisoning | 14,15 |
| 06.   | PtO2, 5 Mole % | Incomplete reaction even after 10 hours, catalyst poisoning | 14,15 |
| 07.   | Pt/C, 50 % wet | Incomplete reaction even after 10 hours, catalyst poisoning | - |

*All the reactions were carried out at 60 to 65°C and at 15 to 20 kg/cm² hydrogen pressure in an autoclave with methanol as a solvent. Reaction progress checked as on TLC.*
It was a challenging task to keep the amount of compound III below 1.0% during reaction itself, if being more than 1.0% it becomes strenuous to remove it during isolation and requires repeated crystallization to achieve impurity profile as per ICH limit in final API [9,10].

To achieve the amount of compound III below 1.0% it was necessary to enhance the reaction rate and specifically acidic medium is accelerating the reduction of pyridine containing compounds. Hence the reaction rate can be increased by addition of conc. HCl to the reaction mixture. The method of conc. HCl addition is not feasible in plant scale which could be cause for autoclave rusting and could be the cause for accidents.

To overcome from the issue, it was decided to prepare the HCl salt of pyridine analog and isolate it in solid form and use it as an input for the reduction reaction. HCl salt ensures the presence of required amount of HCl in the reduction reaction and maintain the pH of reaction mixture. All together the it makes the process easier and plant feasible.

Acidic medium is frequently used in the reduction of pyridines to prevent the inhibition of catalyst by the basic nitrogen atom especially inhibition by the resulting more basic piperidines. Presence of an acid also changes the functional group actually undergoing hydrogenation from pyridine to pyridinium ions. Greater rate of hydrogenation of pyridinium ion may be due to a flat adsorption of the molecule on the catalyst surface, whereas the free base with an unshared pair of electron may adsorbed edgewise [11]. The coordination ability of nitrogen in the pyidine ring was blocked by Hydrochloride salt of compound III, thus the pyridine nucleus in hydrochloride is polarized to be more liable to catalytic hydrogenation. Hypothetical mechanism of catalytic hydrogenation by hydrochloride salt shown in Figs. 4 and 5.

Formation of C probably takes place in 1,4-addition of A, giving the intermediate B. 5,6 double bond is then reduced preferentially over the 2,3 conjugated bond to yield C. Subsequently, C is converted to D. Freebase of compound D was also isolated and identified.

Our optimization experiments began with the hydrogenation of various salts of III using 10% Pt/C as the catalyst and are reported in Table 2. There was only modest conversion for II in several of the entries (Entry 1, 2, 4). Acetate, Formate and aqueous hydrochloride salts of compound III required high loading of catalyst and observed that the rate of reaction was very slow with catalyst poisoning and the formation of undesired side products.
Methane sulphonic acid salt of compound III (Entry 3) provided better rate of reduction, but due to genotoxic alert of methyl sulphonic acid in finished product this pathway was ruled out.

Anhydrous hydrochloride salt of compound III (Entry 5) isolated using ethyl acetate, which facilitated pyridine ring reduction swiftly by increasing solubility of anhydrous salt in methanol. Reduction also rendered chemo-selectivity towards desired product formation. Reaction was completed in 2 hours with as low as 2% of platinum catalyst loading and compound III present in less than 1.0%.

Anhydrous Hydrochloride salt accelerates the reduction of pyridine with minimal amounts of Platinum on carbon 2% of 50% wet at 12kg/cm² hydrogen pressure.

Anhydrous Hydrochloride salt of pyridine from compound - III was reduced within 2 hours in presence of Pt/C. Compound - II was isolated with excellent purity (99.78%) and satisfactory yield (89.4%) (Fig. 6).

### Table 2. Catalytic hydrogenations (10% Pt /C) of various salts of Compound – III

| Entry | Solvent   | Salt                          | Results |
|-------|-----------|-------------------------------|---------|
| 01.   | Methanol  | Formic                        | Incomplete reaction even after 24 hours with high loading catalyst required [12] |
| 02.   | Methanol  | Maleic                        | Incomplete reaction even after 24 hours with high loading catalyst required with Dimethoxy impurity |
| 03.   | Methanol  | Methane sulfonic              | Better reaction rate but possibility of GI alert |
| 04.   | Methanol  | Aqueous hydrochloride         | Incomplete reaction even after 12 hours with high loading catalyst required with Dimethoxy impurity |
| 05.   | Ethyl acetate | Anhydrous hydrochloride     | Reaction complete within 2 hours. |

*All the reactions were carried out at 60 to 70°C and at 12 kg/cm² hydrogen pressure in an autoclave with Platinum catalyst. *Reaction progress checked as on TLC. GI - Genotoxic Impurity
Boric acid catalyzed amide formation from carboxylic acid is a known synthetic approach [13]. Keeping these aspects in mind boric acid was a preferred catalyst. It was observed that highly facile condensation of 2,5-bis(2,2,2-trifluoroethoxy) benzoic acid with 2-amino methyl pyridine was possible when the reaction was carried out in presence of catalytic amount (0.1 eq.) of boric acid. Boric acid activates the carboxylic acid moiety by reducing the electron density at the carbonyl function, which makes the intermediate 1 (Fig. 7) more prone to amine nucleophilic substitution to facilitate the transformation in moderate to good yield.

Thus, in the first step of the synthesis of compound- III, the presence of a catalyst eliminated the need for chemical activation of 2-aminomethyl pyridine and thus use of the hydroxybenzotriazole (HOBt) and N, N'-dicyclohexylcarbodiimide (DCC) reagents was bypassed. Since mole to mole ratio is used and a lot of solid waste is generated during reaction workup. Therefore, these reagents were not suitable at commercial level. Compound - III was isolated as a hydrochloride salt with impurity profile found as per ICH limit with high purity (99.91 %) and satisfactory yield (85.8 %) (Fig. 8).

Flecainide acetate salt is prepared by isolating compound– II as a free base and anhydrous salt is prepared by using acetic acid in methanol, further methanol was distilled out and API was isolated from Isopropyl alcohol with high purity (99.88%) and satisfactory yield (90.8%) (Fig.9) Synthesis of compound I using optimized reaction conditions are depicted in Fig. 10. Impurity profile found at below regulatory limits, and purifications such as column chromatography or repeated crystallization were not required to attain the desired purity.

**Fig. 7. Intermediate 1**

**Fig. 8. Related substance by HPLC (Compound- III)**
Fig. 9. Flecainide acetate (Compound-I) Related substance by HPLC

Commercial Optimised Process

New Isolated Hydrochloride salt of Compound - III

Fig. 10
On the basis of the optimized conditions, the batch was carried on 75 kg scale and the results were reproduced.

4. CONCLUSION

In conclusion our effort resulted into a scalable and highly efficient manufacturing process of Flecainide acetate. Process also encompasses with the usage of a catalytic amount of boric acid reagent for the amidation which by pass the use of traditional reagents which are moisture sensitive in nature and could be the cause reaction incompletion. Hence the boric acid use makes the process cost effective and robust for plant scale up. The synthetic approach introduces a new intermediate with HCl salt compound III, which accelerate the reaction rate and make the process cost effective. The isolation of compound III in salt form ensures the 1 equivalent of HCl and avoid use of excessive HCl which might cause for the autoclave reactor rusting over the period of time after multiple bathes execution.

All together the research explores the short efficient improved, cost effective, convenient, environmentally benign, as well user-friendly process for commercial manufacturing of Flecainide Acetate with high purity. Improvement in catalytic reduction helps in isolation of pure product in short time span.

Supporting Information

Spectral Copies of IR, ESI-MS, $^1$H NMR, $^{13}$C NMR and Elemental analysis of compound I, II, III and ESI-MS, $^1$H NMR of Dimethoxy impurity A (PDF). This material is available after references.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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