A GREEN, LARGE SCALE SYNTHESIS OF FENOPROFEN CALCIUM DIHYDRATE WITH SIMPLE CALCIUM (II) CARBONATE AND WATER

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ABSTRACT

The main objective of this research is to deliver a large-scale manufacturing procedure by using eco-friendly solvents or green solvents. The core invention of this research is fenoprofen calcium complex preparation with non-chlorinated calcium salt known as Calcium carbonate (CaCO_3) in aqueous media without using any organic solvent. This attempt has succeeded without using prior art calcium salt reagents like Calcium chloride (CaCl_2) and Calcium hydroxide (Ca(OH)_2) and these reagents were used with the combination of organic solvents like ethanol or Acetone by earlier researchers. This article will give an eco-friendly process and improved quality material of Fenoprofen calcium dihydrate as per ICH guidelines.

Keywords: Fenoprofen calcium dihydrate, Green synthesis, Calcium salt formation, Calcium carbonate, Water and without organic solvent

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INTRODUCTION

The generic drug substance, which is used for the treatment of symptomatic relief for rheumatoid arthritis, osteoarthritis, and mild to moderate pain, is Fenoprofen calcium dihydrate (1). The author attempted a new method of synthesis to make calcium salt of Fenoprofen with calcium carbonate instead of using other calcium reagents and this attempt was made with green solvent water. The majority of the prior art procedures were reported in organic solvents like Acetone, Ethanol etc.

The author optimized the process in all stages by incorporating commercially available reagents, which are feasible against the mass production of compound 1. Here in scheme 2 of the innovator route which was described the bromination of secondary alcohol with phosphorous tribromide and salt formation was made with stepwise active metal booster methodology with sodium hydroxide¹. Very few pieces of literature were available for the synthesis of chiral pure fenoprofen calcium² and various fenoprofen metal complex compounds preparations to enhance the pharmacological activity of Fenoprofen³.

We developed a single-step salt formation process to reduce the cost and completely removed expensive phosphorous tribromide by substituting a highly inexpensive halogenating reagent Thionyl chloride as described in Scheme-1 of compound 1. It is a commercially scalable process that competes with the market price and in line with all the regulatory specifications requirements.

The main invention in this process is Calcium salt formation with calcium carbonate without organic solvents and hence this final process is so-called green synthesis. The other literature reagents like calcium chloride and calcium hydroxide were corrosive, bit expensive than calcium carbonate.

EXPERIMENTAL

Synthesis of 1-(3-phenoxyphenyl) ethanone (6)

In a clean and dry round bottom flask 500.0 gm of compound 8 was dissolved in 3000.0 mL of N, N-Dimethylformamide under gentle stirring at room temperature (RT). After 10 minutes of stirring it was added 3000.0gm of anhydrous potassium carbonate, 1000gm of compound 7 and 150.0 gm of copper powered, then the reaction mixture temperature was heated and maintained for 8 hours at 150-155°C until its starting material get complies over HPLC monitoring (starting material NMT 2.0%).

Scheme-1: Proposed Route of Synthesis of Compound 1

Scheme-2: Prior Art Literature/ Innovator Route of Synthesis

The reaction mixture was cooled to 25-35°C (RT) and filter the residual potassium carbonate, copper through celite bed. The resulting solution was distilled under reduced pressure; the obtained residue was diluted with O-xylene (5000.0 mL). The organic layer was washed twice with 5% Hydrochloric acid (2x 750.0 mL) followed by 5% Sodium hydroxide (2x750.0mL) and finally washed with saturated sodium chloride. After removal of O-xylene under vacuum, the resulting crude oily mass yield of compound 6 was reported as 720.0 gm (87.03%) with purity NLT 98.0% and any other impurity content NMT 1.0%.

¹H NMR (CDCl₃): δ 2.57 (s, 3H); δ 7.03 (d, 2H); δ 7.14 (t, 1H); δ 7.19-7.22 (dd, 1H); δ 7.36 (t, 2H); δ 7.40 (t, 1H); δ 7.58 (bs, 1H); δ 7.67 (dd, 1H); ¹³C NMR: 26.63, 117.98, 119.02, 123.21, 129.86, 138.77, 156.50, 157.64, 197.32; FT-IR (Cm⁻¹): 3066.23, 3039.80, 1686.05, 1072.46, 1162.34, Mass (M⁺): 213.2 (M⁺: 212.34).

Synthesis of 1-(3-phenoxyphenyl) ethanol (5)

700.0 gm of compound 6 was dissolved in 3500.0 mL of methanol under gentle stirring and then added 93.59 gm of Sodium borohydride portion wise at 0-5°C. Stirred the reaction mass for 2-3 hours at 0-5°C, reaction monitored by HPLC, once reaction complies and then reaction mass quenched in precooled water solution and pH adjusted 6N Hydrochloric acid. The resulting reaction mass was extracted with methylene chloride (3X3000.0 mL). The combined organic layers were washed with saturated sodium chloride and the dried organic layer was removed under reduced pressure. The obtained yield was reported 750.0 gm (98.0%) with purity NLT 99.0% and any other impurity NMT 1.0%.

¹H NMR (CDCl₃): δ 1.47-1.49 (d, 3H); δ 1.77 (d, 1H); δ 4.85-4.90 (m, 1H); δ 6.89-6.91 (dd, 1H); 6.99-7.02 (dd, 2H); δ 7.05 (t, 1H); δ 7.09-7.12 (m, 2H); δ 7.28-7.36 (m, 3H); ¹³C NMR: 25.16, 70.05, 115.79, 117.64, 118.91, 120.10, 123.27, 129.73, 129.77, 147.97, 157.05, 157.43; FT-IR (Cm⁻¹): 3367.29, 3065.49, 3039.46, 1163.85, 1071.70; Mass (M⁺): 214.2 (M⁺: 214.26).

Synthesis of 1-(3-(1-Chloroethyl) Phenoxy) benzene (4)

In a dry round bottom flask 700.0 gm of compound 5 in 4000.0 mL of Methylene chloride and then added 300 gm of Thionyl chloride dropwise at room temperature. Slowly raise the temperature to reflux for 4 to 5 hours, once TLC complies then quench the reaction mass into the water and separate the organic layer. The resulting organic layer is distilled out to get compound 4. Yield reported: 680.0 gm; ¹H NMR (CDCl₃): δ 1.83 (d, 3H); δ 5.01-5.06 (m, 1H); δ 6.90-6.93 (dd, 1H); δ 7.01 (d, 2H); δ 7.08-7.14 (m, 3H); δ 7.25-7.36 (m, 3H); ¹³C NMR: 26.38, 58.11, 116.86, 118.95, 121.15, 123.43, 129.75, 129.86, 144.74, 156.77, 157.39; FT-IR (Cm⁻¹): 3063.89, 3039.90, 1163.22, 693.15; Mass (M⁺): 230.1 (M⁺: 232.71).

Synthesis of 2-(3-phenoxyphenyl) ropane nitrile (3)

In a clean round bottom flask 600.0 gm of compound 4 was dissolved in 2500.0 mL of dimethylsulfoxide followed 159.12 gm of sodium nitrile is added portion-wise. The resulting solution was heated to 70-75 °C and maintain for 6.0 hours until its starting materials gets completed. Once the reaction complies then is quenched in ice-cooled water and extracted with methylene chloride (3X 1000mL). The combined organic layers were washed with saturated sodium chloride solution and then dried over sodium sulfate. The organic layer was distilled to afford compound 3 as a light yellow oil with 650 gm of yield. FT-IR (Cm⁻¹): 3064.66, 3040.21, 2986.75, 2938.83, 2242.48, 1163.58, and 1210.03

Synthesis of 2-(3-phenoxyphenyl)propanoic acid (2)

In a 3L round bottom flask fitted with a reflux condenser and gentle stirrer 600.00 gm of compound 3 was taken in a mixture of 600ml of Ethanol and 900 mL of 50% potassium carbonate under vigorous stirring at room temperature. Heat the reaction mass to 95°C and maintain it for 6-7 hours, after completion of the reaction cool the reaction mass to room temperature and then pH adjusted to 2 with 6N Hydrochloride. The acidic mass was extracted with Ethyl acetate (3X 1200mL), the combined organic layer was washed with saturated sodium chloride and dried over sodium sulfate. Remove the solvent to afford 550 gm of compound 2 as a light yellow oil with purity NLT 99.0 %. ¹H NMR (CDCl₃): δ 1.48 (d, 3H); δ 3.71 (q, 1H); δ 6.85-6.89 (dd, 1H); δ 7.69-7.01 (d, 2H); δ 7.04-7.11 (m, 3H); δ 7.22-7.34 (m, 3H); δ 10.42 (s, 1H); ¹³C NMR: 18.00, 45.18, 117.46, 118.20, 118.94, 122.33, 123.35, 129.74, 129.85, 141.63, 156.89, 157.45, 180.54; FT-IR (Cm⁻¹): 3064.29, 3039.67, 2982.13, 2938.52, 1711.80, 1163.79, 1072.53, 1244.51; Mass (M⁺): 241.1 (M⁺: 242.27).

Synthesis of Calcium 2-(3-phenoxyphenyl) propanoate hydrate (1)

In a round bottom flask 500.00 gm of compound 2 (Fenoprofen) was dissolved in 2500.0 mL of water and 165.25 gm of Calcium carbonate was added portion wise under gentle stirring. Heat the reaction mass temperature to 95°C. Maintain the reaction temperature for 3-4 hours until the reaction complies with TLC.

Fig.-1: ¹H NMR of Compound 1 Fig.-2: ¹³C NMR of Compound 1

Date: Monday, 16 December, 2019

Time: 16:35 India Standard Time

Fig.-3: FT-IR of Compound 1

Once the reaction complies with TLC cool the reaction temperature to 25°C and then further cool to 10-15°C under gentle stirring. Maintain the mass temperature for 45 minutes at 10-15°C. The resulting white precipitate was filtered through the Buckner funnel and the filtered cake was washed with cool water. The wet material was subjected for drying at 75°C and afford 550 gm of Fenopropfen calcium dihydrate with purity NLT 99.0%, any other impurity NMT 0.1%. ¹HNMR (CDCl₃): δ 1.23 (d, 3H); δ 3.40 (m, 1H); δ 6.70(d, 1H); δ 6.93-6.95(d,2H); δ 6.99 (s, 1H); δ 7.06-7.07 (t, 2H); δ 7.15-7.19 (t, 1H); δ 7.31-7.35 (t, 2H); ¹³CNMR: 19.54, 47.60, 115.67, 118.26, 123.05, 123.10, 129.03, 129.91, 146.74, 156.00, 156.88, 180.31; FT-IR (Cm⁻¹): 3066.54, 3037.84, 2978.58, 1420.16, 1442.90, 1162.79, 1245.75; Mass (M^H): 241.13 (M⁺: 242.27).

Fig.-4: Mass Spectra of Compound 1

Fenopropfen Calcium Dihydrate BNo-FPN-VI-009 (Reg No-D-A21900649)

Fig.-5: PXRD of Compound 1

SMS Pharmaceuticals Limited: R&D Center
Sample Information

<Sample Information>

Sample Name : Fenopropfen calcium
 Sample ID : FPN-V/022
 Data Filename : 191211.lcd
 Method Filename : 191210.lcd
 Batch Filename : 191201_056.lcb
 Vial # : 1-5
 Injection Volume : 20 µL
 Date Acquired : 19-12-2019 22:14:26
 Date Processed : 20-12-2019 10:13:30

191211.lcd

Sample Type : Unknown
 Acquired by : Bhanovri Mohan
 Processed by : Ravi teja

<Chromatogram>

<Peak Table>

191211.lcd

Peak#	Ret. Time	RRT	Area	Area%	Name
1	17.57	0.89	5070	0.05	RT:17.606
2	19.28	0.98	3856	0.04	RT:19.315
3	19.65	1.00	9798808	99.67	Fenopropfen calcium
4	26.96	1.37	1662	0.02	RT:27.010
5	27.71	1.41	2265	0.02	RT:27.759
6	29.63	1.51	1496	0.02	RT:29.683
7	33.61	1.71	7653	0.08	RT:33.651
8	33.99	1.73	10547	0.11	RT:34.028
Total			9831356	100.00	

Checked By:
 Date :

Fig.-6: HPLC Chromatograph of Compound 1

CONCLUSION

The outcome of this research has been given an innovative green technology for making Fenopropfen calcium dihydrate (an active pharmaceutical ingredient) with promising commercial value at large scale synthesis since none of the literature was reported the current invention process and the salt formation procedure established in green synthetic pathway such as the water used as a solvent. Therefore the process which is reported in this research article is novel, scalable and economic too.

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