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Synthesis and characterization of potential impurities in Fenofibrate drug substance

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ABSTRACT

Fenofibrate is used to treat high levels of cholesterol and triglyceride in the blood. In the present study, eight process related impurities of Fenofibrate drug were synthesized and characterized by their respective spectral data (IR, MS and ^{1}H-NMR). The identification of these impurities should be useful for quality control in the manufacture of Fenofibrate.

Keywords: Benzophenone derivatives, Fenofibrate, antilipemic, impurity.

INTRODUCTION

The safety of a drug product is not only dependent on the toxicological properties of the active drug substance (or API), but also on the impurities formed during the various chemical synthesis or formulation process or product degradation. Therefore, identification, quantification, and control of impurities in the drug substance or drug product are important parts of drug development for obtaining marketing approval [1-3]. Individual impurity in pure form is required by analytical development department for analytical method development, validation and quality controls for final product release. Impurities can be obtain by active substance degradation and enrichment of desired impurity up to certain level followed by isolation by column chromatography or PREP-HPLC purification. If impurities are identified as process or synthesis related like isomer impurity in starting material, unreacted starting material and derivative of starting material, due to side reactions are not possible to obtain by degradation method. These can be obtained easily by designing proper synthesis route.

Fenofibrate, marketed as Tricor brand name, belongs to the class of fibrates. Fenofibrate reduces bad cholesterol like low density lipoproteins, very low density lipoproteins and triglycerides found in blood. It also increases good cholesterol *i.e.* high density lipoprotein levels[4,5]. Reduction of cholesterol levels in the blood has been shown to reduce the risks associated with heart disease, such as heart attack.

Fenofibrate is an isopropyl ester of fenofibric acid, chemically designated as isopropyl 2-(4-(4-chlorobenzoyl) phenoxy)-2-methylpropanoate. Various synthesis procedures have been provided for Fenofibrate[6]. Thus Fenofibrate can obtain by reaction of 4-chloro-4'-hydroxy- benzophenone with isopropyl 2-bromo-2-methylpropanoate[7], fenofibric acid esterification with 2-bromopropane[8], and recent report *via* decarboxylative arylation[9]. Synthesis of Fenofibrate results in formation of impurities may be as unreacted starting material, side reaction, isomer impurity from starting material, and derivative of them. In this publication our work deals with synthesis and characterization of impurities/ process related substances in Fenofibrate. These impurities are mention in EP and USP pharmacopoeia.

MATERIALS AND METHODS

Analytical

Thin-layer chromatography (TLC) were run on silica gel 60 F254 pre-coated plates (0.25 mm, Merck, Art. 5554) and spots were visualized inside an UV cabinet under short UV. Infrared spectra were recorded on IR Affinity-1, Shimadzu. ^{1}H-NMR spectra were recorded on Bruker Advance III, 400 MHz with TMS as an internal standard. Mass spectra were obtained using LC-MS API-2000, ABSciex. Yields mentioned are from unoptimized reaction condition, of isolated pure product.

Chemicals

All solvents and reagents were purchased from Aldrich (India) and S. D. Fine Chemicals, Mumbai. The solvents and reagents were used without purification.

Synthesis

Preparation of 2-[4-(4-chlorobenzoyl)-phenoxy]-2-methyl- propionic acid (2)

To a stirred solution of Fenofibrate (3.0 g, 0.008 mole) in ethanol (30 ml) was added sodium hydroxide (0.4 g, 0.009 mole) in water (2 ml). The reaction mixture was then stirred at 84 ^{o}C for 3 h. Reaction progress was monitored by TLC (ethyl acetate:hexane, 2:8 v/v, R_f = 0.1). Reaction mixture was cooled to room temperature, concentrated under reduced pressure to get residue which was added to ice cold water (50 ml), acidified with dil. hydrochloric acid. Solid product precipitated out was filtered, dried under air to get white colored solid product. Yield: 2.47 g, 93%. HPLC purity: 97.6%. mp: 179.7^{o}C. IR (cm^{-1}): 2958-2866 (aliphatic-H), 1504 (C=O stretching), 1456, 1367 (aliphatic-H bending), 1253 (C-O-C asymmetric stretching). ^{1}H-NMR ($CDCl_3$): 7.76-7.70 (q, 4H), 7.46-7.44 (d, 2H), 6.96-6.94 (d, 2H), 1.70 (s, 6H). Mass: m/z 319 $[M+H]^+$, 340.8 [M+Na].

General procedure for preparation of (3) and (4)

To a stirred solution of **(2)** (0.5 g, 0.0015 mole) in alcohol (10 ml) was added sulfuric acid (1 ml) and kept under stirring at 80^{o} C for 4 h. Reaction progress was monitored by TLC Reaction mixture was concentrated under reduced pressure to obtain residue which was added to ice cold water (50 ml), extracted with ethyl acetate (2×50 ml). Collected organic layers, washed with saturated sodium bicarbonate solution (100 ml). Organic layer separated, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get white colored solid product.

2[4-(4-Chlorobenzoyl)-phenoxy]-2-methyl propionic acid methyl ester (3)

TLC (ethyl acetate:hexane, 3:7 v/v, R_f = 0.8). Yield: 0.47 g, 90%. HPLC purity: 97.65%. mp: low melting solid. IR (cm^{-1}) 2958-2856 (aliphatic-H), 1751 (ester), 1651, 1585 (C-C stretching aromatic), 1253 (C-O-C asymmetric stretching), 1132, 761, 748 (halides). ^{1}H-NMR ($CDCl_3$): 7.75-7.699 (m, 4H), 7.46-7.44 (d, 2H), 6.86-6.84 (d, 2H), 3.77 (s, 3H), 1.67 (s, 6H). Mass: m/z 333 $[M+H]^+$ and 355 [M+Na].

2[4-(4-Chlorobenzoyl)-phenoxy]-2-methyl propionic acid ethyl ester (4)

TLC (ethyl acetate:hexane, 3:7 v/v, R_f = 0.9). Yield: 1.75 g, 62%. HPLC purity: 97.7%. mp: 70.8^{o}C. IR (cm^{-1}), 1745 (ester), 1654, 1595, 1247 (aliphatic - H bending), 1138 (C-O-C asymmetric stretching), 761, 748 (halide). ^{1}H-NMR ($CDCl_3$): 7.-75-7.68 (q, 4H), 7.46-7.43 (d, 2H), 6.88-6.84 (d, 2H), 4.26-4.21 (q, 2H), 1.69 (s, 6H), 1.25-1.21 (t, 3H). Mass: m/z 347 $[M+H]^+$ and 370 [M+Na].

Preparation of 2-[4-(4-chlorobenzyl)phenyl]-2-methyl propionic acid 1-isopropoxy carbonyl-1-methyl ethyl ester (5)

To a stirred solution of **(2)** (1.16 g, 0.007 mole) in acetonitrile (20 ml) was added potassium carbonate (1.65 g ,0.012 mole) followed by 2-bromo-2-methylpropionic acid (2.0 g, 0.012 mole), reaction mixture was stired at room temperature for 12 h. Reaction progress was monitored by TLC (ethyl acetate:hexane, 5:5 v/v, R_f = 0.1). Reaction mixture concentrated under reduced pressure to give residue which was added to ice cold water (100 ml), extracted with ethyl acetate (2×100 ml). Collective organic layer dried over anhydrous sodium sulfate, filtered concentrated under reduced pressure to get crude reaction mass. Crude reaction mass dissolved in acetonitrile (20 ml) was added potassium carbonate (1.65 g, 0.012 mole) and isopropyl bromide (2.0 g, excess). Reaction mixture was stirred at room temperature for 10 h. Reaction progress was monitored by TLC (ethyl acetate:hexane, 2:8 v/v, R_f = 0.8). Reaction mixture was added to cold water (100 ml), extracted with ethyl acetate (2×100 ml). Collective organic layer dried over anhydrous sodium sulfate, filtered concentrated under reduced pressure to get crude product. Crude product was purified over silica column chromatography to get off white colored solid product. Yield: 0.216 g, 12%. HPLC purity: 97.7%. mp: low melting solid. IR (cm^{-1}) 2983 (aliphatic - H), 1726, 1716 (ester), 1598, 1587 (aliphatic-H bending), 1300, 1286, 1246 (C-O-C asymmetric stretching), 763, 738 (halide). ^{1}H-NMR ($CDCl_3$): 7.75-7.70 (dd, 4H), 7.46-7.43 (d, 2H), 6.94-6.92 (d, 2H), 5.09-5.03 (m, 1H), 1.69 (s, 6H), 1.52 (s, 6H), 1.26-1.24 (d,

6H). Mass: m/z 447 $[M+H]^+$.

Preparation of 4-chloro-4-hydroxy benzophenone (6)

Thionyl chloride (30 ml) was added to 4-chlorobenzoic acid (3.0 g, 0.019 mole), reaction mixture was heated to reflux maintain for 5 h. Reaction mixture was concentrated by down word distillation to obtain acid chloride as gummy residue was dissolved in methylene chloride (20 ml) was added slowly to the solution of aluminum chloride (2.5 g, 0.019 mole) and phenol (1.8 g, 0.019 mole) in methylene chloride (9 ml) at 0 ^oC. Reaction mixture was maintain under nitrogen at room temperature for 14 h. Reaction progress was monitored by TLC (ethyl acetate:hexane, 2:8 v/v, R_f = 0.6). Reaction mass was added to water (100 ml), extracted with methylene chloride (2×100 ml). Combined organic layer dried over anhydrous sodium sulfate, filtered and evaporated to get crude reaction mass. Crude reaction mass was purified by column chromatography to get white colored solid product. Yield: 2.5 g, 56%. HPLC purity: 99.7%. mp: 172.6^oC. IR (cm^{-1}), 3093-2555 (aliphatic-H), 1678 (ketone), 1483 (aliphatic-H bending), 736, 725 and 686 (substituted benzene). ^{1}H-NMR ($CDCl_3$): 7.70-7.66 (dd, 4H), 7.46-7.44 (dd, 2H), 6.92-6.89 (dd, 2H). Mass: m/z 331 $[M-H]^-$.

Preparation of (4-chloro-phenyl)-(4-isopropoxy-phenyl)-methanone (7)

To a stirred solution of **(6)** (2.0 g, 0.008 mole) and potassium carbonate (2.2 g, 0.016 mole) in acetonitrile (20 ml) was added isopropyl bromide (1.0 g, 0.008 mole), maintained under stirring at room temperature for 4 h. Reaction progress was monitored by TLC (ethyl acetate:hexane, 2:8 v/v, R_f = 0.7). Reaction mixture was diluted with water (50 ml), solid formed, filtered and dried to get pale yellow colored solid product. Yield: 1.84 g, 77%. HPLC purity: 99.6%. mp: 108.1 ^oC. IR (cm^{-1}), 2958-2866 (aliphatic-H), 1504, 1456, 1367 (aliphatic-H bending), 1253 (C-O-C asymmetric stretching), 761, 748. ^{1}H-NMR ($CDCl_3$): 7.79-7.78 (d, 2H), 7.77-7.76 (d, 2H), 7.72-7.71 (d, 2H), 7.70-7.69 (d, 2H), 7.46-7.44 (d, 2H), 6.95-6.91 (d, 2H), 1.39-.37 (s, 6H). Mass: m/z 275 $[M+H]^+$ and 297 [M+Na].

Preparation of 3-[4-(4-chloro-benzoyl)-phenoxy]-butan-2-one (8)

To a stirred solution of **(6)** (2.0 g, 0.008 mole) and potassium carbonate (2.2 g, 0.016 mole) in acetonitrile (20 ml) was added 3-chloro-2-butanone (1.0 g, 0.008 mole), stirred at room temperature for 4 h. Reaction progress was monitored by TLC (ethyl acetate:hexane, 2:8 v/v, R_f = 0.5). Reaction mixture was diluted with water (50 ml), extracted with ethyl acetate (2×50 ml). Combined organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to get crude product. Crude product was purified using column chromatography to get off white solid product. Yield: 1.75 g, 66%. HPLC purity: 99.6%. mp: low melting solid. IR (cm^{-1}) 2958-2866 (aliphatic-H), 1504, 1456, 1367 (aliphatic-H bending), 1253 (C-O-C asymmetric stretching), 761, 748. ^{1}H-NMR ($CDCl_3$): 7.80-7.76 (m, 2H), 7.72-7.69 (m, 2H), 7.47-7.44 (m, 2H), 6.93-6.89 (m, 2H), 4.75-4.70-2 (q, 1H), 2.20 (s, 3H), 1.58-1.55 (t, 6H). MS: m/z 302 $[M+H]^+$ and 325 [M+Na].

Preparation of 3-chloro-4-hydroxy benzophenone (9)

To 3-chlorobenzoic acid (3.0 g, 0.019 mole) was added thionyl chloride (30 ml) slowly, reaction mixture heated to reflux, maintain at reflux temperature for 5 h. Reaction mixture was concentrated by downward distillation to obtain residue diluted by methylene chloride (20 ml). It was then added to the solution of aluminum chloride (2.5 g, 0.019 mole) and phenol (1.8 g, 0.019 mole) in methylene chloride (9 ml) at 0 ^oC under nitrogen atmosphere. Reaction mixture was maintain under stirring at room temperature for 10 h. Reaction progress was monitored by TLC (ethyl acetate:hexane, 2:8 v/v, R_f = 0.5). Reaction mixture was diluted with water (100 ml), extracted with methylene chloride (2×100 ml). Combined organic layers dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude reaction mass. Crude mass was purified by column chromatography to get white colored solid product. Yield: 2.5 g, 56%. HPLC purity: 98.7%. mp: 55.2 ^oC. IR (cm^{-1}) 3059 (aliphatic-H), 1732 (ketone), 1589, 1483 (aliphatic-H bending), 736,725 and 686 (substituted benzene). ^{1}H-NMR ($CDCl_3$): 8.21-8.20 (t, 1H), 8.12-8.10 (dd, 1H), 7.657.62 (dd, 1H), 7.50-7.44 (m, 3H), 7.33-7.15 (m, 1H), 7.10-7.0 (dd, 2H). MS: m/z 231 $[M-H]^-$.

RESULTS AND DISCUSSION

Finofibrate API (**1**) is a isopropyl ester of finofibric acid (**2**) while synthesis there are various possibilities of impurity formation. Different pharmacopoeial impurities are synthesized, they are compounds (**2**) to (**9**), structures as mention in **Figure 1**.

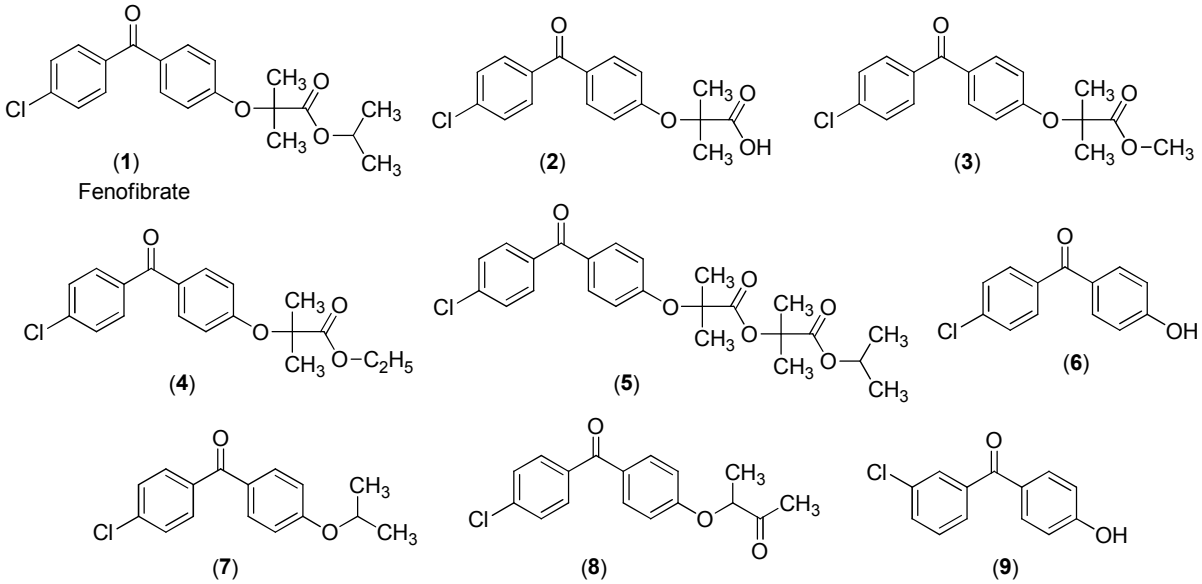
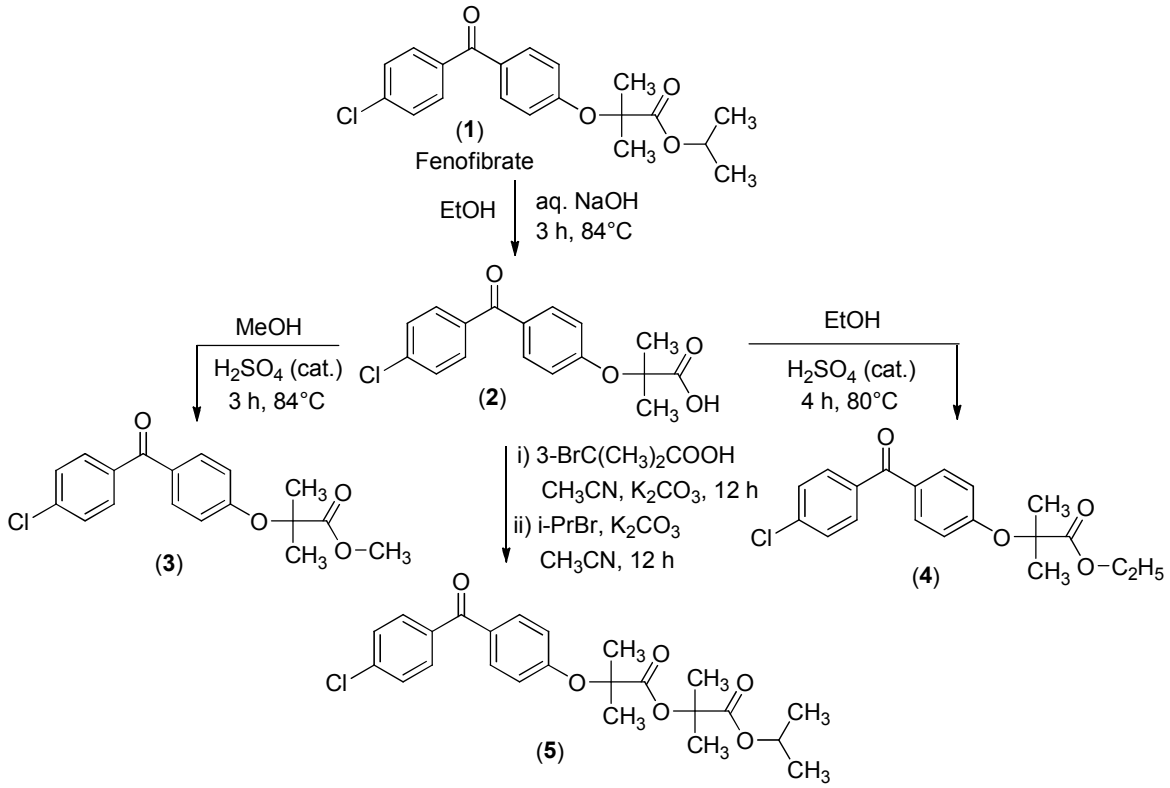


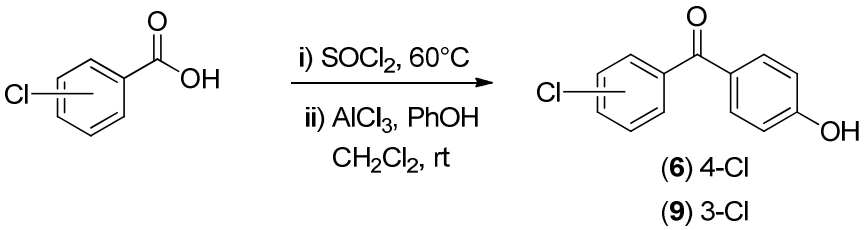
Figure 1: Fenofibrate and its impurities

Finofibric acid (**2**), impurity B as per EP monograph is degradation impurity obtain from Fenofibrate API by base hydrolysis. Finofibric acid methyl ester **(3)** can be synthesized easily from finofibric acid (**2**) by treating with methanol under acid catalyst. Similarly finofibric acid ethyl ester (**4**) synthesized using ethanol. Compound (**3**) and (**4**) are mention in EP monograph as impurity D and E respectively. Compound (**5**) diester, impurity C as per USP monograph was synthesized from finofibric acid (**2**) in two steps. First step involves finofibric acid (**2**) esterification using 2-bromo-2-methylpropionic acid followed by esterification using isopropyl bromide under basic condition. Reaction scheme for synthesis of (**2**) to (**5**) is as mention in **Scheme 1**.



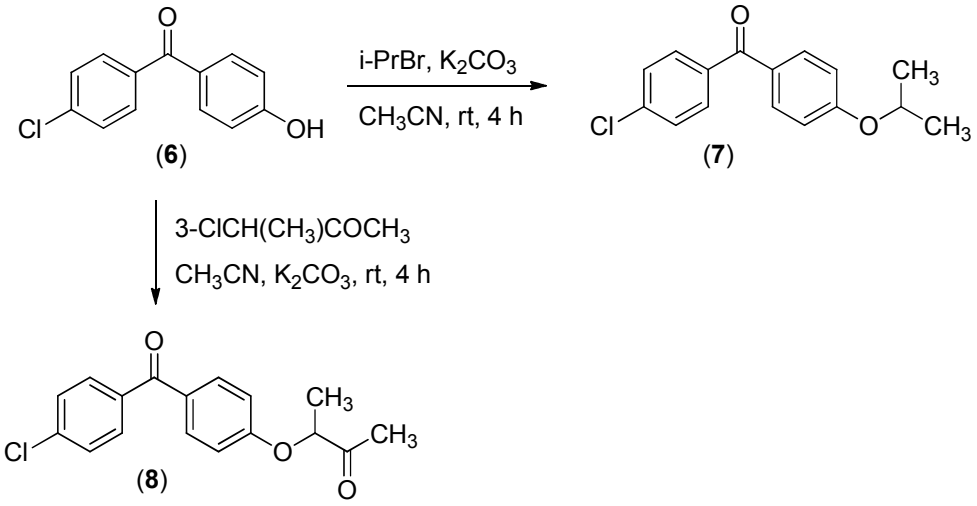
Scheme 1: Synthetic reaction scheme for Fenofibrate impurities (2) to (5)

4-Chloro-4′-hydroxybenzophenone (**6**) and 3-chloro-4′-hydroxybenzophenone (**9**) can be synthesized by Friedel-Crafts acylation of phenol using 4-chlorobenzoyl chloride or 3-chlorobenzoyl chloride respectively, **Scheme-2**.



Scheme 2: Synthesis of 3-chloro-4-hydroxybenzophenone (9)

4-Chloro-4-hydroxybenzophenone (**6**) is synthesized from 4-chlorobenzoic acid under Friedel-Crafts reaction condition same as for (**9**) which is mention in UPS as impurity A. Compound (**9**) on etherification with isopropyl bromide gives compound (**7**), impurity F as per EP monograph. Etherification of (**6**) using 3-chloro-2-butanone yields compound (**8**), impurity F as mention in EP monograph. Synthetic scheme as mention in **Scheme 3**.



Scheme 3: Synthetic reaction scheme for Fenofibrate impurities (7) and (8)

Among all eight Fenofibrate impurities synthesized one is degradation impurity and rest are process related impurities. It was necessary to see all these impurities in same HPLC condition. HPLC details for all eight Fenofibrate impurity is as given in **Table 1**.

Table 1: HPLC chromatogram* retention time data

Sr. No.	Impurity (EP/ USP)	Compound No.	HPLC RT	RRT wrt API
1	A (USP)	6	4.22	0.44
2	B (EP)	2	4.18	0.43
3	C (EP)	8	5.07	0.53
4	C (USP)	5	12.9	1.34
5	D (EP)	3	6.41	0.67
6	E (EP)	4	7.74	0.80
7	F (EP)	7	8.12	0.84
8	3-chloro impurity#	9	7.77	0.81
9	Fenofibrate API	1	9.63	1.0

*Chromatographic conditions: as per USP monograph, column: discovery C18, Supelco, 250×4.6 mm, 5 µm, detector: 286 nm, flow: 1.2 ml/ min, run time: 35 min, column temperature: 35 ^{o}C.
3-Chloro-4′-hydroxybenzophenone

CONCLUSION

In conclusion, eight process related impurities of an active pharmaceutical ingredient, Fenofibrate are synthesized independently. They were fully characterized based on their spectral data. As most of these impurities are mention in pharmacopeia required by analytical development and quality control department.

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REFERENCES

[1] S.J. Ingale, C.M. Sahu, R.T. Paliwal, S. Vaidya, A.K. Singhai, *Int. J. of Pharm. & Life Sci.*, **2011**, 2(7), 955-962.
[2] V.S. Tegeli, G.B. Gajeli, G.K. Chougule, Y.S. Thorat, U.S. Shivsharan, , S.T. Kumbhar, *Int. J. of Drug Form. & Res.*, **2011**, 2(4), 174-195.
[3] B. Misra1, A. Thakur, P.P. Mahata1, *Int. J. of Pharm. Chem.*, **2015**, 5 (7), 232-239.
[4] H. Ling, J. T. Luoma, D. Hilleman, *Cardiology Research*, **2013**, 4(2), 47-55.
[5] M.J. Chapman, *British J. of Diabetes & Vascular Disease*, **2006,** 6 (1), 11-19.
[6] M.Z. Rehman, A.A. Kazi, H.L. Siddiqui, M.A. Kashmiri, V.U. Ahmed, *J. Chem. Soc. Pak.*, **2007,** 29(4), 352-356**.**
[7] J.P. Bourgogne, R. Sornay, **1988**, US4739101 A.
[8] B. Lucas, **2013**, US 8445715 B2.
[9] L. Chu, J.M. Lipshultz, D.W.C. MacMillan, *Angew. Chem. Int. Ed.*, **2015**, 54 (27), 7929–7933.