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IMPURITY PROFILE STUDY OF VENLAFAXINE HYDROCHLORIDE, AN ANTIPSYCHOTIC DRUG SUBSTANCE

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Venlafaxine hydrochloride is a phenyl ethylamine derivative, used for the treatment of depression. During the process development of venlafaxine hydrochloride, six process-related potential impurities were detected in high-performance liquid chromatography. All these impurities were identified, synthesized, and subsequently characterized by their respective spectral data (IR, mass, ^{1}H NMR, and ^{13}C NMR) as described in this article.

Keywords: Antipsychotic; depression; potential impurities; venlafaxine

INTRODUCTION

Venlafaxine hydrochloride (**1**)[1–3] is a potent serotonin–norepinephrine reuptake inhibitor (SNRI) used for the treatment of depression, a common type of psychiatric disorder. This product was developed by Wyeth Laboratories and is currently being marketed under the trade name of Effexor. It is chemically known as RS-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride.

The presence of related compounds or impurities in an active pharmaceutical ingredient (API) can have significant impact on the quality and safety of the drug product. As per the guidelines recommended by ICH,[4] it is a mandatory requirement to identify and characterize all the unknown impurities that are present in an API with a level of >0.10%. Hence, a comprehensive study was undertaken to identify and characterize all the impurities that are present in the API. In this context, the present work describes the impurity profile study of venlafaxine hydrochloride (**1**), which includes identification, synthesis, and spectral characterization.

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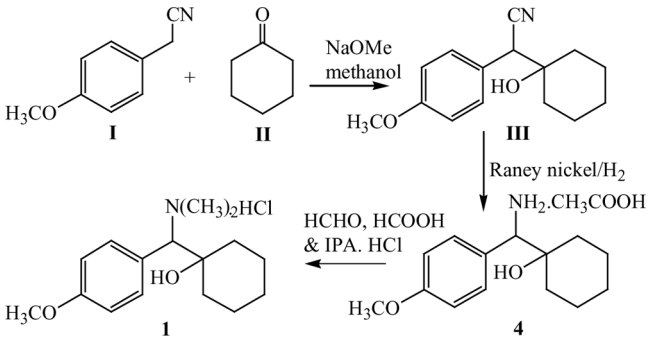
RESULTS AND DISCUSSION

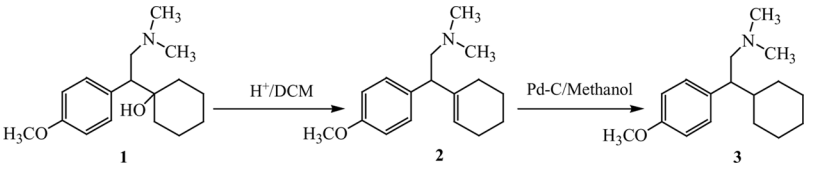
During the process development of venlafaxine hydrochloride (Scheme 1), six process-related potential impurities were detected in high-performance liquid chromatography (HPLC). To identify the molecular weight of the respective impurities, liquid chromatographic–mass spectrometry (LC-MS) was performed.

From the molecular weight information, extensive study was undertaken to synthesize the six impurities. Finally, all these impurities were synthesized and subsequently subjected for spectral analysis [mass, ^{1}H NMR, ^{13}C NMR, and infrared (IR)]. Based on the spectral data, these impurities were characterized as (2RS)-2-(cyclohex-1-enyl)-2-(4-methoxyphenyl)-N,N-dimethyl ethanamine (**2**), (2RS)-2-cyclohexyl-2-(4-methoxyphenyl)-N,N-dimethyl ethanamine (**3**), 1-[(1RS)-1-(4-methoxyphenyl)-2-(methylamino)ethyl] cyclohexanol (**5**), (5RS)-5-(4-methoxyphenyl)-3-methyl-1-oxa-3-azaspiro[5.5]undecane (**6**), (RS)-5-(4-methoxyphenyl)-3-aza-1-oxaspiro[5,5]undecane (**7**),[5] and 2-(4-methoxyphenyl)-N,N-dimethylethanamine (**8**).

The related compound (impurity) **2** was synthesized by acid-catalyzed dehydration of **1** with sulfuric acid (Scheme 2). The mass spectrum of **2** displayed a protonated molecular ion peak at m/z 259.8, which is 18 amu lesser than **1**. In the IR spectrum, a broad band between 3500 and 3300 cm^{-1} corresponding to OH absorption disappeared, which suggests that a water molecule was lost from **1**. In the ^{1}H NMR spectrum, a triplet signal at δ 5.6 ppm corresponding to alkene proton with one proton integration was observed, and it was confirmed because the ^{13}C NMR displayed alkene carbon signals at δ 121.4 and 139.2 ppm. Based on these spectral data, the structure of **2** was confirmed as (2RS)-2-(cyclohex-1-enyl)-2-(4-methoxyphenyl)-N,N-dimethylethanamine. Compound **3** was synthesized by catalytic hydrogenation of **2** using Pd/C (Scheme 2) in methanol as solvent. The mass spectrum of **3** displayed a protonated molecular ion peak at m/z 262.3, which is 2 amu greater than **2**. In the ^{1}H NMR spectrum, a signal at δ 5.6 ppm corresponding to alkene proton disappeared, and signals at 0.9–1.5 ppm corresponding to cyclohexyl group were observed. In the ^{13}C NMR spectrum, signals at δ 121.4 and 139.2 ppm corresponding to alkene carbons disappeared. Based on the spectral data, the structure of **3** was confirmed as (2RS)-2-cyclohexyl-2-(4-methoxyphenyl)-N, N-dimethylethanamine.



Scheme 1. Synthesis of venlafaxine hydrochloride.

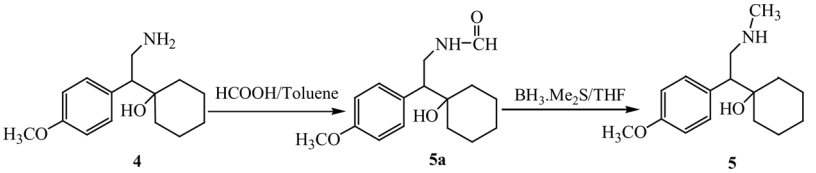


Scheme 2. Synthesis of impurities **2** and **3**.

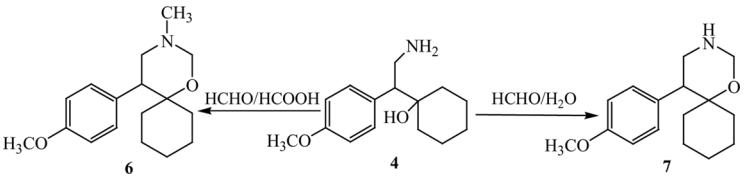
Formylation of **4** using formic acid afforded **5a**, confirmed in mass spectra by a protonated molecular ion peak at m/z 278.2. Compound **5a** was further reacted with $BH_3 \cdot Me_2S$ (Scheme 3) in the presence of tetrahydrofuran (THF) at reflux temperature to yield **5**. The mass spectrum of **5** displayed a protonated molecular ion peak at *m/z* 264.3, which is 14 amu greater than **4**. In the IR spectrum, a week band at 3306 cm^{-1} corresponding to secondary NH absorption was observed. In ^1H NMR spectrum, all signals are similar to that of **4**; in addition to that, a singlet signal at δ 2.7 ppm corresponding to N-CH_3 with three proton integration was observed, which was further confirmed in ^{13}C NMR by a signal at δ 30.8 ppm. Based on these spectral data, the structure of **5** was confirmed as 1-[(1RS)-1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol.

The related compound **6** was synthesized from intermediate **4** by reaction with formaldehyde and formic acid in the presence of water as solvent (Scheme 4) at reflux temperature. The mass spectrum of **6** displayed a protonated molecular ion peak at m/z 276. In the IR spectrum, a broad band between 3500 and 3300 cm^{-1} corresponding to OH absorption disappeared. In the ^1H NMR spectrum, a methylene group attached between NH and oxygen was observed as a quartet at δ 4.4 ppm with two-proton integration, a methyl group attached to nitrogen was observed as singlet at δ 2.4 ppm with three-proton integration, and it was further confirmed in ^{13}C NMR by a signal at δ 39.9 ppm. Based on the spectral data, the structure of **6** was confirmed as (5RS)-5-(4-methoxyphenyl)-3-methyl-1-oxa-3-azaspiro[5.5]undecane.

Reaction of **4** with formaldehyde in the presence of water as solvent (Scheme 4) yielded impurity **7**. The mass spectrum of **7** displayed a protonated molecular ion peak at *m/z* 262.1, which is 12 amu greater than **4**. In the IR spectrum, a broad band between 3500 and 3300 cm^{-1} corresponding to OH absorption disappeared, and a weak band at 3308 cm^{-1} corresponding to secondary NH absorption was observed. In the ^1H NMR spectrum, a methylene group attached between NH and oxygen was observed as a quartet at δ 4.4 ppm with two-proton integration. Based on the spectral data, the structure of **7** was confirmed as (RS)-5-(4-methoxyphenyl)-3-aza-1-oxaspiro[5,5]undecane.



Scheme 3. Synthesis of impurity **5**.



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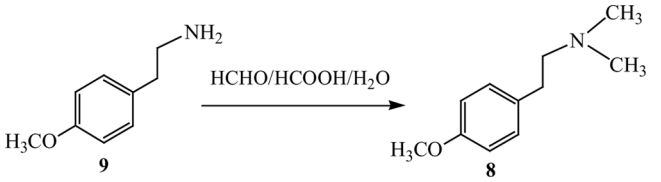
Scheme 4. Synthesis of impurities **6** and **7**.



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Scheme 5. Synthesis of impurity **8**.

2-(4-Methoxyphenyl)ethanamine (**9**) was reacted with formaldehyde and formic acid in the presence of water as a solvent (Scheme 5) to yield impurity **8**. The mass spectrum of **8** displayed a protonated molecular ion peak at m/z 180.9. In the ^{1}H NMR spectrum, the methyl group attached to nitrogen appeared as a singlet at δ 2.8 ppm with six-proton integration and further confirmed in ^{13}C NMR by a signal at δ 42.97 ppm. Based on the spectral data, the structure of **8** was confirmed as 2-(4-methoxyphenyl)-N,N-dimethylethanamine.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury Plus 400-MHz Fourier transform (FT)–NMR spectrometer, and chemical shift values were reported on δ ppm relative to tetramethylsilane (TMS). The ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400-MHz FT-NMR spectrometer, and the chemical shift values were reported on δ ppm relative to $CDCl_3$ and dimethylsulfoxide (DMSO-d_6). The IR spectra were recorded in the solid state as KBr dispersion using a Perkin-Elmer FT-IR spectrophotometer. The mass spectra were recorded on a Shimadzu LCMS-QP8000 instrument. Elemental analysis for CHN was performed on a Perkin-Elmer model 2400 CHNS/O analyzer.

(2RS)-2-(Cyclohex-1-enyl)-2-(4-methoxyphenyl)-N,N-dimethylethanamine (2)

Sulfuric acid (1.0 mL, 0.02 mol) was added slowly to a solution of (RS)-1-[2-dimethyl-amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol (**1**, 5.0 g, 0.02 mol) and dichloromethane (DCM; 30 mL) at 0–5 °C and stirred for 3 h. The pH of the reaction mass was adjusted to 7.5 with saturated aqueous bicarbonate solution (50 mL), and layers were separated. The organic layer was washed with water (25 mL) and concentrated under reduced pressure at less than 45 °C to afford the title compound **2**

(4.1 g, 88.0%). Mass: 259.8 (M^{+1}); IR (cm^{-1}): 3099 (Ar-H), 1611 (C=C); ^{1}H NMR ($CDCl_3$, δ ppm): 7.1 (d, 2H, Ar-H), 6.8 (d, 2H, Ar-H), 5.6 (t, 1H, C=CH), 3.8 (s, 3H, OCH_3), 3.3 (t, 1H, Ph-CH-CH_2), 2.6 (dd, 2H, CH_2), 2.2 [s, 6H, $N(CH_3)_2$], 2.1 (t, 2H, cyclohexene), 1.8 (m, 2H, cyclohexene), 1.5 (m, 4H, cyclohexene); ^{13}C NMR ($CDCl_3$, δ ppm): 157.80, 139.27, 135.34, 128.70, 121.45, 113.53, 62.93, 55.16, 50.08, 45.98, 26.94, 25.35, 22.99, 22.52. CHN analysis calcd. for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found. C, 78.65; H, 9.76; N, 5.47.

(2RS)-2-Cyclohexyl-2-(4-methoxyphenyl)-N,N-dimethylethanamine (3)

To a mixture of **2** (5 g, 0.02 mol) and methanol (50 mL) in an autoclave equipped with hydrogen gas inlet and gas induction stirring system, 5% wet Pd/C (0.5 g) was charged. Temperature was maintained at 40–45 °C for 3 h under 2–3 kg/cm^2 hydrogen gas pressure and then cooled to 25–35 °C. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure at less than 60 °C to afford the title compound **3** (4.6 g, 92.0%). Mass: 262.3 (M^{+1}); IR (cm^{-1}): 3164 (Ar-H) 1245 & 1041 (C-O-C); ^{1}H NMR ($CDCl_3$, δ ppm): 7.1 (d, 2H, Ar-H), 6.9 (d, 2H, Ar-H), 3.8 (s, 3H, OCH_3), 3.6 (m, 1H, Ph-CH-CH_2), 3.3 (dd, 1H, CH_2), 3.0 (dd, 1H, CH_2), 2.2 (s, 6H, $N(CH_3)_2$), 0.9–1.7 (m, 11H, cyclohexyl); ^{13}C NMR ($CDCl_3$, δ ppm): 158.89, 130.99, 129.37, 114.37, 61.22, 55.21, 46.61, 44.65, 43.53, 42.46, 39.13, 31.23, 29.71, 26.14, 26.08, 26.01. CHN analysis calcd. for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 78.16; H, 10.50; N, 5.32.

1-[(1RS)-1-(4-Methoxyphenyl)-2-(methylamino)ethyl]-cyclohexanol (5)

Formic acid (2.2 g, 0.048 mol) was added to a solution of 1-[(RS)-2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol (free base of **4**, 10 g, 0.04 mol) in toluene (60 mL), and the mixture was heated to reflux for 5 h. The reaction mass was cooled to 25–35 °C and washed with saturated aqueous sodium bicarbonate solution (150 mL). The toluene layer was washed with water (2 × 25 mL) and distilled off completely under reduced pressure at less than 70 °C to afford N-[2RS-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethyl]formamide **5a** (11 g, 99%). To a solution of **5a** (11 g, 0.04 mol) in THF (30 mL), 10 mol solution of boranedimethyl sulfide (9.1 g, 0.12 mol) was slowly added and heated to reflux for 5 h. The reaction mass was cooled to 0–5 °C, quenched with methanol (50 mL), and concentrated under reduced pressure at less than 60 °C. The residual product was dissolved in DCM (50 mL) and washed with water (30 mL). The DCM layer was distilled off completely under reduced pressure to afford the title compound **5** (7.7 g, 73%). Mass: 264.3 (M^{+1}); IR (cm^{-1}): 3500–3200 (OH), 3306 (N-H) 1243 & 1039 (C-O-C); ^{1}H NMR ($CDCl_3$, δ ppm): 7.1 (d, 2H, Ar-H), 6.9 (d, 2H, Ar-H), 3.9 (s, 3H, OCH_3), 3.8 (m, 1H, Ph-CH-CH_2), 3.3 (dd, 1H, CH_2), 3.1 (dd, 1H, CH_2), 2.7 (s, 3H, NCH_3), 0.9–1.7 (m, 11H, cyclohexyl); ^{13}C NMR ($CDCl_3$, δ ppm): 158.86, 130.49, 130.17, 113.88, 74.58, 55.24, 52.57, 50.83, 36.87, 33.91, 30.86, 25.36, 21.30, 21.16. CHN analysis calcd. for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found C, 72.91; H, 9.53; N, 5.36.

(5RS)-5-(4-Methoxyphenyl)-3-methyl-1-oxa-3-azaspiro[5.5]-undecane (6)

To a solution of **4** (5 g, 0.02 mol), a free base, in water (50 mL), 36% formaldehyde (4.7 mL, 0.047 mol) and formic acid (3.7 mL, 0.08 mol) were added and heated to 90–95 °C for 60 min. The resultant reaction mass was cooled to 0–5 °C, the pH adjusted to 9.0 with 10% sodium hydroxide solution (30 mL), and the product was extracted with DCM (2 × 100 mL). The DCM layer was washed with water (25 mL) and distilled off completely to afford the compound **6** (3.9 g, 88.0%). Mass: 276 (M^{+1}); IR (cm^{-1}): 3164 (Ar-H) 1250 & 1055 (C-O-C); ^{1}H NMR ($CDCl_3$, δ ppm): 7.1 (d, 2H, Ar-H), 6.9 (d, 2H, Ar-H), 4.4 (q, 2H, O-CH_2-NCH_3), 3.8 (s, 3H, OCH_3), 3.1 (dd, 1H, CH_2), 2.8 (dd, 1H, CH_2), 3.2 (m, 1H, Ph-CH-CH_2), 2.4 (s, 3H, NCH_3), 0.9–1.7 (m, 10H, cyclohexyl); ^{13}C NMR ($CDCl_3$, δ ppm): 158.34, 132.11, 130.32, 113.28, 78.97, 75.48, 55.21, 53.14, 47.22, 39.92, 36.82, 25.82, 24.37, 20.99, 20.41. CHN analysis calcd. for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found C, 74.19; H, 9.11; N, 5.14.

(RS)-5-(4-Methoxyphenyl)-3-aza-1-oxaspiro[5,5]undecane (7)

To a solution of a free base of **4** (5 g, 0.02 mol) in water (30 mL), 36% formaldehyde (5 mL, 0.06 mol) was added, and the mixture was stirred at 25–35 °C for 4 h. The separated solid was filtered, washed with water (15 mL), and dried at 40–50 °C to afford the title compound **7** (4.9 g, 93%). Mass: 262.1 (M^{+1}); IR (cm^{-1}): 3308 (N-H), 1242 & 1022 (C-O-C); ^{1}H NMR ($CDCl_3$, δ ppm): 7.1 (d, 2H, Ar-H), 6.9 (d, 2H, Ar-H), 4.4 (q, 2H, O-CH_2-NCH_3) 3.8 (s, 3H, OCH_3), 3.6 (dd, 1H, CH_2), 3.4 (dd, 1H, CH_2), 2.9 (m, 1H, Ph-CH-CH_2), 0.9–1.7 (m, 11H, cyclohexyl); ^{13}C NMR ($CDCl_3$, δ ppm): 158.3, 132.1, 130.3, 113.2, 78.9, 75.4, 55.2, 53.1, 47.2, 39.9, 36.8, 25.8, 24.3, 20.9, 20.4. C H N analysis calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C,73.55; H, 8.83; N, 5.33.

2-(4-Methoxyphenyl)-N,N-dimethylethanamine (8)

To a solution of **9** (5 g, 0.033 mol) in water (50 mL), 36% formaldehyde (8.3 mL, 0.10 mol) and formic acid (7.6 mL, 0.16 mol) were added, and the mixture was heated to 90–95 °C for 12 h. The resultant reaction mass was cooled to 0–5 °C, pH was adjusted to 9.0 with 10% sodium hydroxide solution (30 mL), and the product was extracted with DCM (2 × 100 mL). The DCM layer was washed with water (25 mL) and distilled off completely to afford the compound **8** (4.8 g, 82%). Mass: 180.9 (M^{+1}); IR (cm^{-1}): 3011 (Ar-H), 1251 & 1025 (C-O-C); ^{1}H NMR ($CDCl_3$, δ ppm): 7.2 (d, 2H, Ar-H), 6.9 (d, 2H, Ar-H), 3.8 (s, 3H, OCH_3), 2.8 (s, 4H, Ar-CH_2-CH_2-N), 3.2 [s, 6H, $N(CH_3)_2$]; ^{13}C NMR ($CDCl_3$, δ ppm): 158.78, 129.62, 127.48, 114.37, 59.26, 55.24, 42.97, 29.91. CHN analysis calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.76; H, 9.50; N, 7.78.

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REFERENCES

1. Yardly, J. P.; Morris Hosbands, G. E.; Stack, G.; Butch, J.; Bicksler, J.; Moyer, J. A.; Muth, E. A.; Andree, T.; Fletcher, III, H.; James, N. G.; Sielecki, A. R. 2-Phenyl-2-(1-hydroxycycloalkyl) ethylamine derivatives: Synthesis and antidepressant activity. *J. Med. Chem.* **1990**, *33*, 2899–2905.
2. Morris Husbands, G. E.; Yardly, J. P.; Muth, E. A. 2-Phenyl-2-(1-hydroxycycloalkyl or 1-hydroxycycloalk-2-enyl) ethylamine derivatives. US Patent 4,535,186, 1985.
3. Morris Husbands, G. E.; Yardly, J. P.; Muth, E. A. Substituted phenylacetonitriles. US Patent 4,611,078, 1986.
4. ICH. *Guideline Q3A (R): Impurities in new drug substances.* February 7, 2002.
5. Basappa; Kavitha, C. V.; Rangappa, K. S. Simple and an efficient method for the synthesis of 1-[2-dimethylamino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol hydrochloride: (+)-Venlafaxine racemic mixtures. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3279–3281.