Synthesis of related substances of Tramadol hydrochloride, analgesic drug

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ABSTRACT

Tramadol hydrochloride is a mild, non-addictive, centrally acting binary analgesic agent, during the process development of Tramadol hydrochloride, four related substances (Impurities) were observed along with the final API. Those impurities were identified as, [2-(3-methoxyphenyl)cyclohex-1-enyl]-N,N-dimethylmethanamine hydrochloride (6), (1RS)-[2-(3-methoxyphenyl)cyclohex-2-enyl]-N,N-dimethylmethanamine hydrochloride (7), (3-((1R,2R)-2-((dimethylamino)methyl)-1-hydroxy cyclohexyl)phenol hydrochloride (9) and 3,3’-Dimethoxy-biphenyl (11). Present work describes the synthesis and characterization of all these four impurities.

Keywords: Active pharmaceutical ingredients, Analgesic, Tramadol hydrochloride, related substances, synthesis

INTRODUCTION

Tramadol hydrochloride [(±)cis-2-[(dimethylamino)methyl]1-(3-methoxyphenyl) cyclohexanol hydrochloride] is a mild, non-addictive, centrally acting binary analgesic agent, introduced in Germany in the late 1970s by Grunenthal.¹ It was approved for use in the United States in 1995 and is currently marketed as Ultram by Ortho-McNeil Pharmaceuticals, Inc. While the marketed form is the racemic hydrochloride salt of the cis-isomer²-⁴.

![Cis-Tramadol HCl(RR, SS) 1](image)

Tramadol hydrochloride is a very weak µ-opioid receptor agonist, induces serotonin release, and inhibits the reuptake of norepinephrine.⁵,⁶ Tramadol is converted to O-desmethyltramadol, a significantly more potent µ-opioid agonist. The opioid agonistic effect of tramadol and its major metabolite(s) is almost exclusively mediated by such
µ-opioid receptors. This further distinguishes tramadol from opioids in general (including morphine), which do not possess tramadol's degree of receptor subtype selectivity and which are much stronger opiate-receptor agonists. Similarly, the habituating properties of tramadol (such as they are) are arguably mainly due to µ-opioid agonism with contributions from serotonergic and noradrenergic effects.

The identification of impurities and/or degradants in pharmaceuticals is critically important for reasons of both product efficacy and patient safety. The impurities may evoke any form of adverse response, either pharmacologic or toxicologic in patients undergoing medication. Hence to ensure patient safety, impurity profiling of any API and/or degradation product present at > 0.1% is desirable for drugs dosed at < 2 g/day. For drugs dosed at > 2 g/day, the threshold for isolation and identification is lower at 0.05% according to ICH guidelines.

EXPERIMENTAL SECTION

Material and Methods: All reagents and solvents employed were of commercial grade and were used as such, unless otherwise specified. Reaction flasks were oven-dried and heated at 200°C; flame-dried and flushed with dry nitrogen prior to use. All moisture and air-sensitive reactions were carried out under an atmosphere of dry nitrogen. TLC was performed on Kieselgel 60 F254 silica-coated aluminium plates (Merck) and visualized by UV light (λ = 254 nm) or by spraying with a solution of KMnO₄. Organic extracts were dried over anhydrous Na₂SO₄. The melting points were determined in an open capillary tube using a Büchi B-540 melting point instrument and were uncorrected. The IR spectra were obtained on a Nicolet 380 FT-IR instrument (neat for liquids and as KBr pellets for solids). HPLC (Agilent technologies, 1200series). NMR spectra were recorded with a Varian 300 MHz Mercury Plus Spectrometer at 300 MHz (¹H). Chemical shifts were given in ppm relative to trimethylsilane (TMS). Mass spectra were recorded on Waters quattro premier XE triple quadrupole spectrometer using either electron spray ionisation (ESI) or atmospheric pressure chemical ionization (APCI) technique.

Synthesis of [2-(3-methoxyphenyl)cyclohex-1-enyl]-N,N-dimethylmethanamine hydro chloride (impurity 6)
A solution of I(25.0 g, 0.189 mol) in concentrated hydrochloric acid (125.0 mL) was heated at 90–100 °C for 14–15 h. The reaction mass was cooled to room temperature and diluted with water (100.0 mL), extracted with DCM (50.0 mLx3). The solvent was removed by vacuum distillation to get the crude material, which was dissolve in IPA, pH was adjusted to 1.8-2.0 using 20% IPA.HCl solution, the resulting solution was stirred for 15-30 minutes at 25-30 °C. Removal of solvent under reduced pressure gave a residue, which was recrystallized in ethyl acetate to provide 6 (10.0 g, yield 65 %; purity by HPLC 86.83%); IR: (KBr, cm−1) 3006 (Ar CH); 1579 (Ar C=C); 1486 (Ar C=C); 1319(C-N); 1263 (C-O).¹H NMR: (DMSO-d₆) 1.6-1.9 (m, 3H); 2.04 (m, 1H); 2.2 (t, 2H); 2.45-2.83(m, 7H); 3.0-3.15 (m, 2H); 3.54 (d, 1H); 3.92 (s, 3H); 6.6 (t, 1H); 6.8(dd, 2H); 7.3(s,1H); 13C NMR (400MHz) (CDCl₃) δ (ppm):16.3,22.23,22.48,27.96,33.18,42.60,55.26,59.97,112.28,113.83,120.01,123.49,130.00,143.18,145.05, 159.85; ESI-MS: (m/z): 246.42(M⁺+1); mp: 122–124°C.

Synthesis of (1RS)-[2-(3-methoxyphenyl)cyclohex-2-enyl]-N,N-dimethylmethanamine hydro chloride (impurity 7)
A solution of I(50.0 g, 0.189 mol) in concentrated hydrochloric acid (250.0 mL) was heated at 80–85 °C for 14–15 h. The reaction mass was cooled to room temperature and Adjusted pH - 10.0 with diluted sodium hydroxide solution, and the mixture was extracted with DCM(100.0 x 2mL).Organic layer was dried over sodium sulphate. Solvent was distilled off under reduced pressure to obtain the title compound 7 as a residue, which was dissolve in IPA; pH was adjusted to 1.8-2.0 using 20% IPA.HCl solution. The resulting solution was stirred for 15-30 minutes at 25-30 °C,removal of solvent under reduced pressure gave a residue, which was recrystallized in ethyl acetate to provide 7 (10.0 g, yield 65 %; purity by HPLC 90.32%); IR: (KBr, cm−1) 3055 (=C-H ); 1579 (Ali C=C); 1486 (Ar C=C); 1321 (C-N); 1263 (C-O);1083(C-C); 1H NMR: (DMSO-d₆) 1.6-1.9 (m, 3H); 2.04 (m, 1H); 2.2 (t, 2H); 2.45-2.82 (m, 7H); 3.0-3.15 (m, 2H); 3.83 (s,3H); 6.4 (t, 1H); 6.65–6.83 (m, 4H); ¹³C NMR (400MHz) (CDCl₃)δ(ppm):17.41,25.47,25.58,32.55,41.52,45.78,55.25,60.21,112.47,112.51,118.46,129.83,131.02,136.07,142.58,159.94; ESI-MS: (m/z): 246.42, mp: 122–124°C; ESI-MS: (m/z): 246.42(M⁺+1); mp: 77–80°C.
Synthesis of (3-((1R,2R)-2-((dimethylamino)methyl)-1-hydroxycyclohexyl)phenol hydro chloride (impurity 9)
To a solution of 8 (30.0 g, 0.11 mol) in DCM (150.0 mL) was added a solution of boron tribromide in DCM (71.4 g, 0.28 mol) at (-)50 to (-)55°C and maintained for 1-2 h (-)50 to (-)55°C. After completion of the reaction, the reaction mass was quenched with ice-cold water (100.0 mL) and extracted with MTBE (35.0 mL x 4). The combined the organic layers and dried over sodium sulphate. Solvent was distilled off under reduced pressure to obtain the title compound 9 as a residue, which was dissolve in MTBE, pH was adjusted to 2.0-2.2 using 20% IPA.HCl solution. The resulting solution was stirred for 15-30 minutes at 25-30°C. The separated solid was filtered and washed with MTBE (purity by HPLC 80%) , which was recrystallized in 3:1 mixture of MTBE and ethyl acetate (100.0 mL) to give the pure product 9 (6.6 g, yield 96.6%; purity by HPLC 94.57%); IR: (K Br, cm⁻¹) 3410 (O-H); 3276 (Ar O-H); 3029 (Ar C-H); 2921 (C-H); 1614 (Ar C=C); 1293 (C-N); 1069 (C-C); 1H NMR: (DMSO-d6) 10.21 (s, 1OH); 9.2 (s, 1OH); 7.1 (t, 1H); 6.95 (s, 1H); 6.9 (d, 1H); 6.65 (d, 1H); 2.92 (dd, 1H); 2.6-2.8 (m, 7H), 2.3(t, 1H), 1.6-1.9(m, 7H), 1.21-1.73(m, 2H); 13C NMR (400MHz) (DMSO-d6) δ (ppm): 10.90, 21.14, 24.57, 26.15, 38.87, 39.08, 41.20, 44.79, 59.37, 73.70, 112.34, 113.27, 115.50, 128.90, 149.68, 157.22; ESI-MS: (m/z): 250.43 (M⁺+1); mp: 183–189°C.

Synthesis of 3,3’-Dimethoxy-biphenyl (impurity 11)
To a solution of 3 (25.0 g, 0.133 mol) in THF (70.0 mL) were added trisopropyl borate (40.21 g, 0.213 mL) followed by n-BLi in THF 1.6M (13.60 g, 0.28 mol) at (-)65 to (-)70°C and maintained for 4-5 h (-)65 to (-)70°C. After completion of the reaction (18.4 g, 0.133 mol). Quench the reaction mass with diluted hydrochloric acid (10.0 mL). It was extracted with ethyl acetate (50.0 mL x 2). Solvent was distilled off under reduced pressure to obtained residue taken for next step. The residues dissolve in dimethyl ether (DME) under nitrogen atmosphere, was added meta-bromoansaole (25.0 g, 0.133 mol), potassium carbonate (56.8 g, 0.26 mol) and Palladium tetrakis [bis triphenylphosphine Pd(O)] (3.0 g, 0.002 mol) at room temperature. The resulting mixture was heated to 80–85°C and maintained for 12-13 h. After completion of the reaction, solvent was distilled off completely. The residue was added ethyl acetate (50.0 mL) followed by water (100.0 mL) and the resulting mixture was stirred for 10 minutes. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50.0 mL). The combined the organic layers were washed with water (50.0 mL) and the resulting organic layer was dried over sodium sulphate. Solvent of under reduced pressure gave a residue (10.0 g, yield 65 %; purity by HPLC 78%), which was taken for highvacuum distillation (HVD) at 160°C and bath temperature 195°C, to get pure fraction 11 (4.50 g, yield 65 %; purity by HPLC 98.88%); IR: (KBr, cm⁻¹) 3055 (Ar C-H); 1600 (Ar C=C); 1234 (C-O); 1051 (C-C); 1H NMR: (DMSO-d6) 3.9 (s, 6H); 6.9 (d, 2H); 7.6 (d, 2H); 7.13 (d, 2H); 7.38 (d, 2H); 7.38 (d, 2H); 13C NMR (400MHz) (CDCl₃) δ (ppm): 55.26, 112.78, 112.92, 119.68, 129.69, 142.60, 159.87; ESI-MS: (m/z): 215.14 (M⁺+1).
RESULTS

During the process for the synthesis of 1, four impurities were observed. However, as far as we are aware, the syntheses of these four impurities were not reported so far. Herein, we wish to discuss identification, synthesis, and characterization of these four impurities of 1. The HPLC chromatogram, Figure 2, shows the impurity profile of 1.

![HPLC chromatogram of Tramadol hydrochloride](image)

Initially, 1 was subjected to LCMS to learn about the number of contaminants associated with it. Apart from the molecular ion peak of 1, four more peaks with distinct molecular ions were observed in LCMS (Figure 3). Based on the molecular ion peaks, the structure of impurity 6, 7, 9 and 11 has been already reported in the literature, surprisingly its synthesis was not accounted. In this report syntheses and characterization of all the four impurities of 1 will be discussed in detail.

![LC-MS chromatogram of impurity (6)](image)

![LC-MS chromatogram of impurity (7)](image)
The synthesis of [2-(3-methoxyphenyl)cyclohex-1-enyl]-N,N-dimethylmethanamine hydrochloride impurity 6, is described in Scheme 2. Tramadol hydrochloride 1 was subjected to dehydration using concentrated hydrochloric acid, at 90-100°C. Reaction conditions afforded the impurity 6 in good yield and 86.3% HPLC purity. The structure of 6 was confirmed by spectral analysis.
The (1RS)-[2-(3-methoxyphenyl)cyclohex-2-enyl]-N,N-dimethylmethanaminehydrochloride7 has been synthesized according to the synthetic sequence shown in Scheme 3. Tramadol hydrochloride 1 was subjected to dehydration using concentrated hydrochloric acid, at 80-85°C reaction conditions afforded the impurity 7 in good yield and 93.6% HPLC purity. The structure of 7 was confirmed by spectral analysis.

![Scheme 3: Synthesis of impurity (7)](image)

**FIGURE 9: HPLC chromatogram of impurity (7).**

Preparation of (3-((1R,2R)-2-((dimethylamino)methyl)-1-hydroxycyclohexyl)phenol hydrochloride impurity 9, originated from base of 1. demethylation of 8 with borantribromide in methylene dichloride at (-)50 to (-)55°C under nitrogen conditions provided the corresponding demethylation impurity 9 in good yield and 93.6% HPLC purity. The structure of 9 was confirmed by spectral analysis.

![Scheme 4: Synthesis of impurity (9)](image)
The synthesis of 3,3'-Dimethoxy-biphenyl impurity 11 commenced from the meta bromo anisole which is one of the intermediates in the synthesis of 1 (Scheme 1). Originated from 3, metabolic acid of 3 with trisopropyl borate, n-BuLi in methylene dichloride and Tetrahydrofuran at (-)55°C to (-)60°C under nitrogen conditions 10, which on condensation with metabolonic anisole using Tetakis(triphenylphosphine)palladium(0) catalyst in presence of DME and methanol provided impurity 11 in good yield and 95.6% purity. The structure of 11 was confirmed by standard spectral analysis.

![HPLC chromatogram of impurity (9).](image1.png)

**FIGURE 10: HPLC chromatogram of impurity (9).**

**SCHEME 5: Synthesis of impurity (11)**

![HPLC chromatogram of impurity (11).](image2.png)

**FIGURE 11: HPLC chromatogram of impurity (11).**

**TABLE 1: Impurity RRT.**

<table>
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<th>Entry number</th>
<th>Impurity</th>
<th>RRT by HPLC</th>
<th>Purity by HPLC (%)</th>
<th>Mass(m/z) value by LC-MS</th>
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<td>86.83</td>
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<tr>
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</table>
Finally, all the impurities 6,7,9 and 11 were individually co-injected with the API 1 in the HPLC and the HPLC data was compared with that of the API 1. As expected, all the impurities were matching with the impurity profile of 1.

CONCLUSION

These process-related impurities of Tramadol hydrochloride (1) are confirmed by chemical synthesis and characterization using analytical tools such as HPLC, £H NMR, IR, mass, and melting point.

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REFERENCES