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Synthesis and Characterization of Impurities Listed in United States Pharmacopeia of Risperidone Tablets

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ABSTRACT

A very simple and efficient synthesis of three impurities of Risperidone tablets named Risperidone-cis-N-oxide, Risperidone-trans-N-oxide and Bicyclorisperidone mentioned in Unites States Pharmacopeia (USP) of Risperidone tablets has been presented in this manuscript. These three impurities were synthesized and fully characterized on the basis of mass, proton and carbon spectra.

Keywords: Risperidone N-oxide, Bicyclorisperidone, Impurities, Synthesis.

I. INTRODUCTION

Risperidone is an antipsychotic agent belonging to 3-piperidinyl-l-,2-benzisoxazole derivative and has chemical name 3-[2-[4-(6-fluoro-l,2-benzisoxazol-3-yl)-l-piperidinyl]ethyl]-6,7,8,9- tetrahydro-2-methyl-4H-pyrido[l,2-a]pyrimidin-4-one. It is an antipsychotic compound having combined serotonin ($5\text{-}HT_2$) and dopamine (D_2) receptor antagonist effects which plays an important role in the treatment of schizophrenia[1, 2]. Schizophrenia is one of the most severe and debilitating major psychiatric diseases. The introduction of antipsychotic drugs was indisputably a great advance in the pharmacotherapy of mental disorders. There are many advantages offered by Risperidone over typical antipsychotic drugs like faster onset of antipsychotic action, a lower incidence of extrapyramidal effects and greater efficacy against the negative symptoms of schizophrenia [3, 4].

Today, one of the main challenges for the pharmaceutical industry is to develop new drugs that are safe, effective and of high quality when they reach the patients[5]. Impurity profiling (identification and quantification) of a drug plays an important role in order to meet the challenges to ensure high degree of purity of drug substances and drug products[6, 7]. The important and sometimes critical step in impurity profiling is the synthesis of impurity standards that could be useful for analytical method development and validation purpose[8].

In this context, we have undertaken the synthesis of three United States Pharmacopeia (USP) listed impurities of Risperidone tablets named Bicyclorisperidone, Risperidone trans-N-oxide and Risperidone cis-N-oxide[9]. The synthesis and characterization of these impurities have not been reported so far in the literature. These impurities were first synthesized in high purity, characterized by Mass, NMR and further confirmed by their relative retention time (RRT) when injected in HPLC system applying same chromatographic conditions as *described* in USP monograph of Risperidone tablets.

II. RESULTS AND DISCUSSION

Synthesis of all three impurities was carried out from Risperidone sample. Treatment of Risperidone with 30% H_2O_2 in methanol for around 48 hrs gave the mixture of two oxidative products i.e. mixture of cis- and trans-Risperidone N-oxide Figure 1.

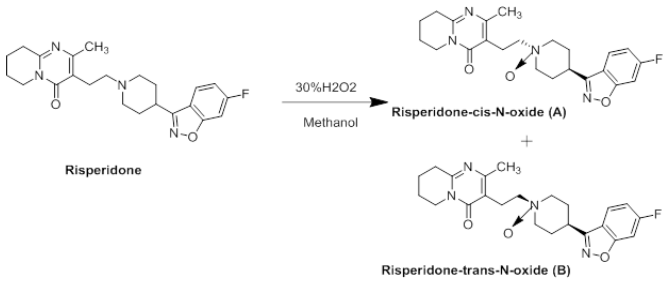

Figure 1. synthesis of Risperidone cis/trans-N-oxide

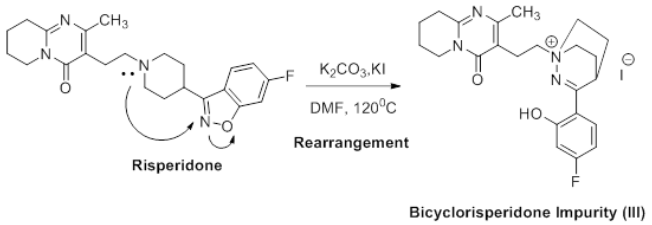

Figure 2. Synthesis of Bicyclorisperidone

The reaction was monitored on thin layer chromatography (TLC; 2% Methanol in MDC). After complete conversion of Risperidone into oxides, the mixture of oxides was subjected to flash chromatography for their separation. To assign cis and trans they were injected in HPLC system with the same conditions as mentioned in USP monograph. On comparing RRT values of these oxides with standard values mentioned in USP monograph, we designated cis (RRT: 1.81)and trans (RRT: 1.65)to the obtained oxides. It was observed that the oxide which came above as compared to another oxide on TLC was cis (less polar) and the later one was trans-oxide (more polar).

For further confirmation, characterization was carried out using mass and NMR spectra. ESI mass spectra of theses oxides was recorded and for both M^+ ion peaks appeared at 427.215, which corresponds to the addition of one oxygen atom in Risperidone molecule. ^1H and ^{13}C-NMR was taken and compared with Risperidone. In both oxides, the ^1H and the ^{13}C chemical shifts of the methylene groups attached to the nitrogen atom in the piperidine ring found to be deshielded when compared to those of Risperidone. Further, in trans-oxide the equatorial protons of methylene group were observed with higher value of chemical shift (δ= 3.71 ppm) when compared to cis-oxide (δ= 3.39 ppm). Rest, not much difference was observed in their δ values.

Synthesis of Bicyclorisperidone was achieved by heating Risperidone in the presence of potassium carbonate and potassium iodide (as a catalyst) in DMF at 120°C for 30-34 hrs. It seems that Risperidone undergoes Boulton-Katritzky type rearrangement[10, 11] under such conditions and converted into Bicyclorisperidone Figure 2.

Conversion was around 30-40%. After isolating Bicyclorisperidone using flash chromatography in 95% purity, it was injected in HPLC system with the same conditions as mentioned in USP monograph and on comparison of RRT value of Bicyclorisperidone (RRT: 0.68) with standard value mentioned in USP monograph, its formation was predicted.

For further confirmation, characterization was done by recording ESI mass spectra and ^1H NMR spectra. Mass spectra of this impurity showed m/z at 411.222 corresponds to exact mass of bicyclo cation and m/z 411.22 also refers to the M^+ molecular ion peak of Risperidone molecule. Both bicyclo and Risperidone has same number of protons and equal to 27. Now to confirm the formation of bicyclo cation impurity i.e. Bicyclorisperidone, its proton and carbon NMR was taken and compared with Risperidone. Bicyclic cation formation was clearly understood by seeing the chemical shift values of methylene protons of piperidine ring. Their values increased from 1.99 to 3.29/3.19 because of positive charge on nitrogen atom. Methylene protons attached to N^+ also shifted to downfield (3.28 ppm) as compared to Risperidone (2.45 ppm). Also CH proton of piperidine ring in bicyclo impurity shifted to upfield (1.18 ppm) as compared to Risperidone (2.98 ppm). All these chemical shifts confirm the formation of Bicyclorisperidone impurity.

III. EXPERIMENTAL

General procedure for the synthesis of Risperidone *cis* and *trans*-N-oxides:

Synthesis of Risperidone-N-oxides has been carried out as shown in Figure 1. To the solution of 2 g of Risperidone in 40 ml methanol, 10 ml of 30% hydrogen peroxide was added. Reaction mixture was maintained at 30-35 °C for 48 hrs. Reaction progress was monitored on TLC (2% Methanol in MDC). After completion of reaction, mixture was distilled out under vacuum at 30°C. 100 ml of water was added to obtained residue

and extracted twice with 100 ml of methylene dichloride. 3 g of residue was obtained which contained mixture of cis and trans-N-oxide. Now this mixture was subjected to flash chromatography (Combiflash) and *cis/trans*-N-oxides were separated. *Cis*-N-oxide (Impurity-I) weight obtained was 1 g and *trans*-N-oxide (Impurity-II) weighed 0.20 g.

Characteristic data of Risperidone *cis*-N-oxide (Impurity-I):

^{1}H NMR (MeOD, 400 MHz, δ ppm): 7.98(dd, J= 8.4Hz, J= 6.8 Hz, Ar1H), 7.43 (dd, J = 8.4 Hz, J= 2.0 Hz, Ar1H), 7.19-7.24(m, Ar1H), 3.75(t, 2H, J= 6.2Hz, -CH_2NCO), 3.58-3.61(m, 4H, -NCH_2CH_2), 3.52-3.39(m, 3H, CH and 2–$NCH_{equi.}$ of piperidine ring), 3.14-3.18(m, 2H, 2–$NCH_{axial.}$ of piperidine ring), 2.90(t, 2H, J=6.6 Hz, CH_2C=N), 2.75-2.2.81(m, 2H, 2–$NCH_2CH_{equi.}$of piperidine ring), 2.40(s, 3H), 2.13-2.17(m, 2H, 2–NCH_2CH_{axial} of piperidine ring), 1.89-2.05(m, 4H, -CCH_2CH_2C); ^{13}CNMR (MeOD, 400 MHz, δ ppm): 165.7, 164.0, 163.9, 163.2, 162.7, 160.1, 159.7, 158.2, 123.0, 122.8, 116.9, 116.0, 112.4, 112.2, 96.9, 96.6, 68.0, 63.1, 42.9, 31.7, 30.6, 29.4, 24.8, 21.3, 19.6, 19.5, 18.5.Characteristic data of Risperidone *trans*-N-oxide (Impurity-II): ^{1}H NMR (MeOD, 400 MHz, δ ppm): 7.94 (dd, J = 8.4 Hz, J= 5.0 Hz, Ar1H), 7.42(dd, J= 8.6Hz, J= 1.8 Hz, Ar1H), 7.18-7.23(m, Ar1H), 3.75(t, 2H, J= 6.2Hz, -CH_2NCO), 3.71-3.74(m, 3H, CH and 2–$NCH_{equi.}$ of piperidine ring), 3.38-3.42 (m, 4H, -NCH_2CH_2), 3.05-3.10(m, 2H, 2–$NCH_{axial.}$ of piperidine ring), 2.89 (t, 2H, J= 6.6 Hz, CH_2C=N), 2.67 (bs, 2H, 2–$NCH_2CH_{equi.}$of piperidine ring), 2.37(s, 3H, CH_3), 2.25-2.28(m, 2H, 2–$NCH_2CH_{axial}$of piperidine ring), 1.87-2.01(m, 4H, -CCH_2CH_2C); ^{13}CNMR (MeOD, 400 MHz, δ ppm): 165.7, 163.8, 163.6, 163.2, 162.7, 159.5, 158.1, 123.0, 122.9, 117.2, 115.9, 112.5, 112.3, 96.8, 96.5, 63.0, 62.7, 42.9, 30.6, 29.3, 24.9, 21.3, 19.6, 19.5, 18.4.

General procedure for the synthesis of Bicyclorisperidone (Impurity-III)

To the solution of 2 g of Risperidone in 10 ml of dimethylformamide, 1.35 g of potassium carbonate and 0.08 g of potassium iodide was added. Reaction mixture was heated at 120 °C and refluxed for 30-35 h. Reaction was monitored on TLC. After completion of reaction, mixture was distilled out under vacuum at 50°C. Residue obtained was loaded on column chromatography to obtained pure 0.05 g of Bicyclorisperidone using 10% methanol/MDC as eluent system Figure 2. ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 6.81-6.93(m, 1H), 6.92(d, J= 10 Hz, 1H), 7.59 (dd, J = 8.8 Hz, J= 7.2Hz, 1H), 4.0-4.016(m, 2H, -CH_2NCO), 3.74-3.82(m, 6H, -N^+ $(CH_2)_3$), 3.07-3.09(m, 2H, -CH2CCO), 2.79 (t, 2H, J= 6.4 Hz, -CH_2C=N), 2.28(s, 3H, CH_3), 1.77-1.86(m, 8H, -$N^+CH_2CH_2$, -$N^+CH_2CH_2$ and -CCH_2CH_2C), 1.23-1.28(m, 1H, CH); ^{13}CNMR (DMSO-d_6, 400 MHz, δ ppm): 166.6, 164.6, 162.7, 162.2, 155.2, 153.0, 132.2, 116.0, 114.4, 108.3, 104.1, 64.6, 59.1, 46.8, 35.0, 31.4, 26.3, 22.7, 21.6, 20.4, 18.5, 16.1.

IV. CONCLUSION

Keeping in view the importance given by different regulatory authorities to impurity profiling of Drug substance/Drug product, we decided to synthesize three USP listed impurities of Risperidone tablets whose synthesis and characterization have not been reported so far and also characterized them successfully.

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VI. REFERENCES

[1]. Reynolds, G. P. Ther. Adv. Psychopharmacol. 2011, 1, 197-204.
[2]. He, H.; Richardson, J. S.International Clinical Psychopharmacology, 1995, 10, 19-30.
[3]. Marder, S. R.; Meibach, R. C. Am. J. Psychiatry. 1994, 151, 825-35.
[4]. Miyamoto, S.; G E Duncan, G. E.; Marx, C. E.; Lieberman, J. A. Molecular Psychiatry, 2005, 10, 79–104.
[5]. Paul, S. M.; Mytelka, D. S.; Christopher T. Dunwiddie, C. T.; Persinger, C. C.; Munos, B. H.; , Lindborg, S. R.; Schacht, A. L. Nature Reviews Drug Discovery, 2010,9, 203-214.
[6]. Holm, R.; Elder, D. P. Eur. J. Pharm. Sci. 2016, 87, 118-135.
[7]. International Conference on Harmonisation, ICH (2006) Q3B (R2): Impurities in new drug product.
[8]. International Conference on Harmonisation, ICH (2005) Q2B (R1): Validation of analytical procedures: Text and methodology.
[9]. USP monograph: Risperidone Tablets, USP38-NF33, Pharmacopeial forum, 32(4), 1109.

[10]. Raymond, C. F. Jones.; Chatterley, A.; Marty, R.; Owton, W. M.; Mark, R. J. Elsegood, Chem. Commun., 2015, 51, 1112-1115.
[11]. J. J. Li, Name Reactions, 4th ed., 2009, 62-63.