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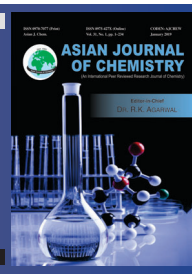

Oxidative Degradation of Paliperidone Using Potassium Permangnate in Acid Medium

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Oxidative degradation reactions of paliperidone are studied using potassium permanganate in acidic medium spectrophotometrically. Complete reaction was carried out in pseudo first order condition. The reaction orders were calculated with respect to the paliperidone and acid, the obtained values indicate that these reactant have less than first order dependency on the reaction rate. Oxidation products were identified using LC-MS technique and their *m/z* values were found to be 207, 221 and 443. Kinetics and the mechanism of the reactions were derived from the results identified. The reactions were studied at four different temperatures with different paliperidone and acid concentrations. The activation and thermodynamic parameters were calculated by graphical method.

Keywords: Kinetics, Paliperidone, Oxidative degradation, Mechanistic study.

INTRODUCTION

Potassium permanganate is a well-known oxidizing agent [1] widely used in the in the oxidation reactions, synthetic as well as in the analytical methods [2]. The reaction medium signifies the pathway of oxidation [3], as we know that permanganate constitutes +2 to +7 states of manganese ion, among these Mn^{7+} is prominent oxidizing agent [4-6]. Similar study of degradation of pharmaceutical drugs has been studied by using different oxidant systems [7-10].

9-Hydroxyrisperidone (paliperidone, m.f. $C_{23}H_{27}N_4O_3F$, molar mass 426.48 g/mol) is a drug which is a dopamine antagonist and 5-HT2A antagonist. This drug is a characteristic antipsychotic class of medicine [11-13]. It is used in the treatment of mania and at lower doses as maintenances for bipolar disorder and used also in the treatment of schizophrenia and schizoaffective disorder [14]. Its bioavailability is 28 % [15]. This study has been undertaken as there was no degradation study of paliperidone was carried out using any oxidizing agents.

EXPERIMENTAL

The analytical grade chemicals are used throughout the experiments. Deionized water is used for preparing all solutions. The required proportion of a substance in a mixture of standard potassium permanganate solution is obtained by dissolving weighed quantity of $KMnO_4$ in deionized water. Similarly, stock solution of paliperidone is prepared by using appropriate amount of drug substance in 25 mL of 0.1N HCl and diluted with deionized water to make it to 0.01M solution. The kinetic measurements were carried out by using CARY 50 Bio make, UV-Vis Spectrophotometer while the pH measurements were performed on Elico make pH meter.

Procedure: The reaction kinetic and spectroscopic measurements have been carried out at constant ionic strength by maintaining pseudo first order conditions. Potassium permanganate is used at least ten times less molar concentrations with respect to paliperidone to maintain pseudo first order reaction condition. Paliperidone and $KMnO_4$ solutions are maintained at constant temperature and mixed together to initiate the reaction by keeping

other reaction conditions constant. Constant temperature (25 ± 0.1 ºC) is maintained throughout the experiment. The progress of the reaction is monitored by measuring change in the absorbance of $KMnO_4$ with respect to time. The chemical reaction is carried out in a 1 cm quartz cell using UV-visible spectrophotometer at 525 nm, λ_{max} of $KMnO_4$. The Beer-Lambert law has been verified for $KMnO_4$ at absorption maximum 525 nm between 1.0×10^{-4} to 1.0×10^{-3} by maintaining specified reaction conditions. The molar absorbance coefficient calculated and is found to as $\varepsilon = 2357$ dm^3 mol^{-1} cm^{-1}. The graph between log $[A_t - A_\infty]$ *versus* time is plotted and values are used in calculation of pseudo first-order rate constants (k_{obs}). Where A_∞ is the absorbance of unreacted $KMnO_4$ at infinite time which does not include Mn(VI) absorbance produced as one of the reaction product and A_t is a absorbance of $KMnO_4$ at any time 't'. The reaction is followed up to the three-fourth reaction completions. The plots obtained over 75 % completions of reaction are linear. The rate constants calculated are reproducible within the error of ± 4 %.

RESULTS AND DISCUSSION

Oxidation products of paliperidone: The LC-ESI-MS is used for the analysis of reaction products in the solution form. The LC-ESI-MS obtained indicate the presence of three major products. The identified molecular ions have *m/z* values as 207, 221 443 and 427, where *m/z* 427 is a molecular ion of paliperidone. The *m/z* 207, 221 and 443 are shown in the **Scheme-I**. These identified products with above said *m/z* values were also found earlier as oxidation reaction products [16] and stress degradation products of paliperidone [17].

Reaction orders: The plots of log k_{obs} *versus* log (conc.) are used to determine the orders of $KMnO_4$, paliperidone and acid. The concentrations of oxidant, reductant and hydrochloric acid varied by maintaining other reaction conditions constant to determine the orders of the each variant. Spectral behaviour during oxidation of paliperidone by $KMnO_4$ at 25 ºC is observed.

Variation of [oxidant]: Keeping paliperidone concentration and ionic strength of a reaction mixture constant, the $KMnO_4$ concentration varied from 3×10^{-5} mol dm^{-3} to 3×10^{-4} mol dm^{-3} concentration. The values are represented in Table-1, which shows that the order with respect to permanganate is unity. The linear plots obtained by pseudo-first order graph (figure not shown) showing constant rate constants at differentpermanganate concentrations under these conditions also verifies the unit order dependency of the permanganate.

Variation of [paliperidone]: Paliperidone concentration was changed in the range from 3×10^{-2} mol dm^{-3} to 3×10^{-3} mol dm^{-3} (Table-1). The effect of this variation on the rate of the reaction is observed at fixed concentrations of $KMnO_4$ and at a fixed ionic strength. It is found that k_{obs} values increased as the concentration of paliperidone is increased. This shows the dependency of the reaction on paliperidone concentration. The slope obtained from the plot of log k_{obs} *vs*. log [paliperidone] is 0.87 indicating less than first order dependence of paliperidone concentration on the rate of reaction.

TABLE-1
EFFECT OF VARIATION OF $[MnO_4^-]$, [PP] AND $[H^+]$ ON THE OXIDATION OF PALIPERIDONE BY $HMnO_4$ AT 25 °C

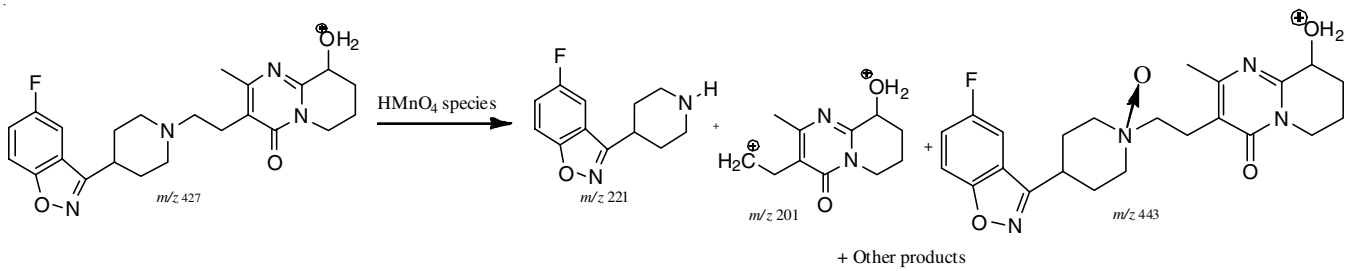
$[KMnO_4] \times 10^4$ (mol dm^{-3})	$[PP] \times 10^2$ (mol dm^{-3})	$[HCl] \times 10^2$ (mol dm^{-3})	$k_{obs} \times 10^{-3}$ (s^{-1})
0.50	3.00	5.00	2.6
1.00	3.00	5.00	2.4
2.00	3.00	5.00	2.6
2.50	3.00	5.00	2.7
3.00	3.00	5.00	2.5
4.00	3.00	5.00	2.4
3.00	0.40	5.00	0.4
3.00	0.70	5.00	0.7
3.00	1.00	5.00	0.9
3.00	2.00	5.00	1.8
3.00	3.00	5.00	2.5
3.00	4.00	5.00	2.8
3.00	3.00	0.06	1.3
3.00	3.00	0.08	1.5
3.00	3.00	0.10	1.7
3.00	3.00	0.50	2.1
3.00	3.00	2.00	2.4
3.00	3.00	3.00	2.6
3.00	3.00	5.00	2.7

[PP] = Paliperidone

Variation of [acid]: The acid concentration varied from 4×10^{-3} mol dm^{-3} to 1×10^{-2} mol dm^{-3} at constant concentrations of paliperidone and $KMnO_4$ at 25 ºC (Table-1).The variation of acid does showed less effect on the reaction rate. The order of the acid concentration is calculate and found as 0.16.

Effect of change in dielectric constant and ionic strength: The dielectric constant of reaction mixture is changed by changing the volume ratio of *t*-butanol in water by keeping reaction conditions constant. The *t*-butanol did not react with permanganate in the present reaction conditions. The graph of log k_{obs} *versus* concentration of *t*-butanol ($r > 0.983$) was linear and the rate constant k_{obs} decreases with decrease in the polarity of the reaction mixture. Ionic strength of the reaction mixture is varied by increasing $[KMnO_4]$ from 0.1 to 0.6 M. Quantifiable change on rate constant is not observed with the variation of ionic strength.

Effect of [manganate]: The effect of initially added MnO_4^-, one of the reaction products is studied by varying manganate



Scheme-I: Oxidation reaction products of paliperidone by $KMnO_4$ in acid medium

concentration from 3×10^{-5} to 3×10^{-4} at constant concentrations of permanganate did not shows any significant effect.

Variation of temperature: The permanganate-paliperidone redox reaction is carried out at four dissimilar temperatures by changing the [paliperidone] and [acid] solution. Ionic strength and other conditions in the reaction mixture are kept constant during this temperature variation. During reaction, the rate constant k observed is increased with increase in temperature. $1/k_{obs}$ *vs.* 1/[paliperidone] and $1/k_{obs}$ *vs.* 1/[HCl] plots are plotted at dissimilar temperature and slopes and intercepts of these graphs are used to calculate rate constant k of the slow step (**Scheme-II**). Thermodynamic parameters are evaluated for the different rate constants at different temperatures by using the Arrhenius equation. The graph of log k *vs.* 1/T is plotted and evaluated energy of activation. Activation parameters obtained are given in Table-2.

$$MnO_4^- + H^+ \underset{}{\overset{K_1}{\rightleftharpoons}} HMnO_4$$

$$HMnO_4 + PP \underset{}{\overset{K_2}{\rightleftharpoons}} \text{Complex (C)}$$

$$\text{Complex (C)} \xrightarrow[\text{slow}]{k} \text{Products}$$

Scheme-II

TABLE-2
ACTIVATION AND THERMODYNAMIC PARAMETERS FOR THE OXIDATION OF PALIPERIDONE USING POTASSIUM PERMANGANATE IN ACID MEDIUM WITH RESPECT TO SLOW STEP OF THE SCHEME

Effect of temperature		Activation parameters	
Temp. (K)	10^3 k s^{-1}	Parameters	Values
293	2.5	$E_a^{\#}$ (kJ mol^{-1})	30.05 ± 1
298	3.3	$\Delta H^{\#}$ (kJ mol^{-1})	24.7 ± 1
303	3.8	$\Delta S^{\#}$ (J $K^{-1}mol^{-1}$)	-398.3 ± 5
313	5.7	$\Delta G^{\#}$ (kJ mol^{-1})	68.5 ± 5
Equilibrium constants K_1 and K_2 at different temperatures			
Temp. (K)	K_1 (dm^3 mol^{-1})	K_2 (dm^{-3} mol^{-1})	
293	2.2	1.9	
298	2.8	2.6	
303	2.9	2.7	
313	4.9	4.5	
Thermodynamic quantities using K_1 and K_2 values			
Quantities	Using K_1 values	Using K_2 values	
ΔH (kJ mol^{-1})	-2.51	-2.51	
ΔS (J K-1mol^{-1})	221.64	184.96	
ΔG (kJ mol^{-1})	-69.4	-58.3	

The expected active oxidizing ions of $KMnO_4$ in acidic medium are $HMnO_4$, $H_2MnO_4^+$, $HMnO_3$ and Mn_2O_7. Out of these permanganate ions, MnO_4^- is the powerful species in low pH medium and Mn(II) is found to be the most stable oxidation reaction product of MnO_4^- is below 7 pH solution. As order with respect to acid concentration is less than unity in aqueous acid medium, $HMnO_4$ from permanganate ion acts as an active species [18]. $HMnO_4$ is the most reactive and more productive species of Mn(VII) in comparison with permanganate ion [19]. The rate of reaction is supposed to reach a threshold value at higher concentrations of H^+ ion indicated that in the acid permanganate protonated form is more active [19]. The equilibrium of the reaction is represented in eqn. 1:

$$MnO_4^- + H^+ \rightleftharpoons [HMnO_4^-] \quad (1)$$

Stoichiometry of the reaction follows 2:1 oxidant and substrate ratio *i.e.* two molecules of permanganates are required for the complete oxidation of one molecule of paliperidone in the acidic medium. This shows pseudo unit order dependency on oxidant and less than first order dependency on [paliperidone] and $[H^+]$ of acid medium. The oxidation products found are Mn(II), 5-fluoro-3-(piperidin-4-yl)benzo[d]isoxazole with *m/z* 221 is formed by the loss of *m/z* 207 molecule from the *m/z* 425. It is confirmed by the fragment found at *m/z* 207. One more fragment is found at *m/z* 443 indicating the formation of N-oxide molecule. At first MnO_4^- reacts with H^+ so as to form $HMnO_4$. Thus formed $HMnO_4$ reacts with paliperidone forming complex these two are known to be fast step later complex breaks and oxidation products are formed by the oxidation reaction. In this reaction, the breaking of complex considered as a slow and rate determining step and is explained in the following mechanism.

Mechanism is proposed for the reaction and based on the experimental study for the oxidation of paliperidone using $KMnO_4$ in acidic medium:

$$\text{Rate} = \frac{-d[MnO_4^-]}{dt} = kK_1K_2[MnO_4^-][PP]_f[H^+]_f \quad (2)$$

Total $[MnO_4^-]$ is

$$[MnO_4^-]_T = [MnO_4^-]_f + [HMnO_4] + [\text{complex}]$$
$$= [MnO_4^-]_f + K_1[MnO_4^-][H^+] + K_1K_2[MnO_4^-][H^+][PP]$$
$$= [MnO_4^-]_f (1 + K_1 [H^+] + K_1K_2[H^+][PP]$$

$$[MnO_4^-]_f = \frac{[MnO_4^-]_T}{(1 + K_1[H^+]) + K_1K_2[H^+][PP]} \quad (3)$$

where f stands for free and T stands for total.

Total $[H^+]$ is given as:

$$[H^+]_T = [H^+]_f + [HMNO_4] + [\text{Complex}]$$

when very low concentrations of $[MnO_4^-]$ and [paliperidone] are used then,

$$[H^+]_T = [H^+]_f \quad (4)$$

Likewise,

$$[PP]_T = [PP]_f \quad (5)$$

Substituting eqns. 3 and 5 in eqn. 2 we get:

$$\text{Rate} = \frac{kK_1K_2[MnO_4^-][PP]_f[H^+]_f}{1 + K_1[H^+]_f + K_1K_2[PP]_f[H^+]_f} \quad (6)$$

$$\frac{\text{Rate}}{[MnO_4^-]} k_{obs} = \frac{kK_1K_2[PP]_f[H^+]_f}{1 + K_1[H^+]_f + K_1K_2[PP]_f[H^+]_f} \quad (7)$$

The eqn. 7 can be rearranged as given below and also verifies and confirms obtained orders with respect to different variations.

$$\frac{1}{k_{obs}} = \frac{1}{kK_1K_2[PP]_f[H^+]_f} + \frac{1}{kK_2[PP]_f} + \frac{1}{k} \quad (8)$$

Eqn. 8 indicates that at constant conditions, plots $1/k_{obs}$ *vs.* 1/[paliperidone] gives a straight line with positive slope

and intercept values at four different temperatures. Similarly, $1/k_{obs}$ *versus* $1/[H^+]$ gives a straight line with positive slope and positive intercept at three assorted temperatures. Thermodynamic quantities and rate constants K_1 & K_2 evaluated using slopes and intercepts found from the graphs of $1/k_{obs}$ *versus* 1/[paliperidone] and $1/k_{obs}$ *vs.* $1/[H^+]$. The values calculated are in good agreement with the earlier values.

Thermodynamic entities for the equilibrium steps K_1 and K_2 of **Scheme-II** are calculated by given procedure. The [paliperidone] and $[H^+]$ are varied at dissimilar temperatures. Using slopes and intercepts of the linear plots of $1/k_{obs}$ *versus* 1/[paliperidone] and $1/k_{obs}$ *versus* $1/[H^+]$, the values of K_1 and K_2 are evaluated and listed in Table-2.

As we know that van′t Hoff equation relates the variation in equilibrium constants with change in temperature, the van't Hoff plots, log K_1 *vs.* 1/T ($r \geq 0.989$, $S \leq 0.01$) and log K_2 *vs.* 1/T ($r \geq 0.972$, $S \leq 0.0087$) are plotted for the variations of K_1 and K_2 with temperature. For the first and second equilibrium steps, enthalpy (ΔH), entropy (ΔS) and free energy (ΔG) of the reaction are calculated (Table-2). By comparing values from K_2 with the values evaluated for the slow step, one can concluded that these values primarily refer to the rate limiting step. This indicates that the reactions earlier slowest step of the reaction are fast with less activation energies [20,21].

The typical quantities obtained for activation parameters, $\Delta S^{\#}$ and ΔH are advantageous for electron transfer reactions. The obtained value of $\Delta S^{\#}$ specifies that radical reaction may not be feasible [22]. The complex (C), intermediate formed during reaction is well-ordered than the reactants because $\Delta S^{\#}$ value is negative [23]. This oxidation reaction seemingly proceeds through following inner sphere mechanism as values of entropy of activation, enthalpy of activation are lower and rate constant of slow step is higher [24].

The thermodynamic and activation parameters revealed that the reaction is favorable in room temperature, as we know that ΔS is positive, ΔH and ΔG are negative which indicated that the reaction is spontaneous.

Conclusion

The degradative oxidation of drug paliperidone by potassium permanganate in the presence of acid medium forms lower masses of degradation products. These formed products are less harmful to the nature and domestic presence of acid condition in the reaction is mandatory. The activation energy of the reaction is less and the first step that is formation of $HMnO_4$ and formation of complex found to take place at faster rate in comparison with complex breaking step. The reactants and reagents utilized in the reaction are environmentally friendly hence can be used in the purification of water and in the wastewater treatment. Insoluble manganese dioxide formed during the reaction provides important role in the elimination of phenols, phenol derivatives and other organic wastes present in the water.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. R.M. Kulkarni, M.S. Hanagadakar, R.S. Malladi, B. Santhakumari and S.T. Nandibewoor, *Prog. React. Kinet. Mech.*, **41**, 245 (2016); https://doi.org/10.3184/146867816X14696298762238.
2. S.R. Melo, M. Homem-de-Mello, D. Silveira and L.A. Simeoni, *PDA J. Pharm. Sci. Technol.*, **68**, 221 (2014); https://doi.org/10.5731/pdajpst.2014.00974.
3. S. Caron, R.W. Dugger, S.G. Ruggeri, J.A. Ragan and D.H.B. Ripin, *Chem. Rev.*, **106**, 2943 (2006); https://doi.org/10.1021/cr040679f.
4. D.C. Bilehal, R.M. Kulkarni and S.T. Nandibewoor, *J. Mol. Catal.*, **232**, 21 (2005); https://doi.org/10.1016/j.molcata.2005.01.020.
5. K.A. Thabaj, S.D. Kulkarni, S.A. Chimatadar and S.T. Nandibewoor, *Polyhedron*, **26**, 4877 (2007); https://doi.org/10.1016/j.poly.2007.06.030.
6. R. Skibinski, L. Komsta and T. Inglot, *Biomed. Chromatogr.*, **30**, 894 (2016); https://doi.org/10.1002/bmc.3625.
7. L. Das, S.K. Barodia, S. Sengupta and J.K. Basu, *Int. J. Environ. Sci. Technol.*, **12**, 317 (2015); https://doi.org/10.1007/s13762-013-0466-y.
8. K.K. Nanda, W.D. Blincoe, L.R. Allain, W.P. Wuelfing and P.A. Harmon, *J. Pharm. Sci.*, **106**, 1347 (2017); https://doi.org/10.1016/j.xphs.2017.01.025.
9. K.A. Attia, N.M. El-Abassawi, A. El-Olemy and A.H. Abdelazim, *New J. Chem.*, **42**, 995 (2018); https://doi.org/10.1039/C7NJ03809G.
10. M. Markiewicz, C. Jungnickel, S. Stolte, A. Bialk-Bielinska, J. Kumirska and W. Mrozik, *J. Hazard. Mater.*, **324**, 428 (2017); https://doi.org/10.1016/j.jhazmat.2016.11.008.
11. S. Edoardo and C. Rosalia, *J. Cent. Nerv. Syst. Dis.*, **3**, 27 (2011).
12. M. del P. Corena-McLeod, A. Oliveros, C. Charlesworth, B. Madden, Y.Q. Liang, M. Boules, A. Shaw, K. Williams and E. Richelson, *Brain Res.*, **1233**, 8 (2008); https://doi.org/10.1016/j.brainres.2008.07.021.
13. R.B. Patel, M.R. Patel, K.K. Bhatt and B.G. Patel, *Anal. Methods*, **2**, 525 (2010); https://doi.org/10.1039/b9ay00276f.
14. N. Yasui-Furukori, M. Hidestrand, E. Spina, G. Facciola, M.G. Scordo and G. Tybring, *Drug Metab. Dispos.*, **29**, 1263 (2001).
15. V. Devra, A. Jain and S. Jain, *World J. Pharm. Res.*, **4**, 963 (2014).
16. D.S. Sanjay and U.B. Vijaya, *J. Pharm. Res.*, **6**, 39 (2013).
17. S.A. Jadhav, S.B. Landge, S.L. Jadhav, N.C. Niphade, S.R. Bembalkar and V.T. Mathad, *Chromatogr. Res. Int.*, **Article ID 929876** (2011); https://doi.org/10.4061/2011/929876.
18. L. Kotai, I. Gacs, I.E. Sajo, P.K. Sharma and K.K. Banerji, *Trends Inorg. Chem.*, **11**, 25 (2009).
19. J.C. Bailar, H.J. Emeleus, R. Nyholm and A.F.T. Dickenson, Comprehensive Inorganic Chemistry, Pergamon Press Ltd.: New York, p. 771 (1975).
20. D.C. Bilehal, R.M. Kulkarni and S.T. Nandibewoor, *Can. J. Chem.*, **79**, 1926 (2001); https://doi.org/10.1139/v01-173.
21. L.N. Jattinagoudar, K.S. Byadagi, S.T. Nandibewoor and S.A. Chimatadar, *Synth. React. Inorg. Met.-Org. Nano-Met. Chem.*, **45**, 1138 (2015); https://doi.org/10.1080/15533174.2013.862684.
22. C. Walling, Free Radicals in Solution, Academic Press: New York, p. 38 (1957).
23. Z.D. Bugarcic, S.T. Nandibewoor, M.S.A. Hamza, F. Heinemann and R. van Eldik, *J. Chem. Soc., Dalton Trans.*, 2984 (2006); https://doi.org/10.1039/B516771J.
24. S.A. Farokhi and S.T. Nandibewoor, *Tetrahedron*, **59**, 7595 (2003); https://doi.org/10.1016/S0040-4020(03)01148-7.