

Kinetics and Mechanistic Investigation of Ru(III) Catalyzed Oxidative Degradation of Linezolid by Permanganate at Environmentally Relevant pH

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The influences of [permanganate], [linezolid], $[Ru^{3+}]$, pH, temperature, ionic strength, solvent polarity, *etc.* on the rates of uncatalyzed and Ru^{3+} catalyzed oxidative degradation of linezolid by Mn^{7+} were investigated at environmentally relevant pH. The increase in [permanganate], [linezolid] and temperature increases the rates of uncatalyzed and catalyzed reactions. It is observed from the calculated pH dependent second order constants that the rate of reaction decreases with increase in pH from 3.0 to 9.0. The values of apparent second order rate constants are 12 times faster in the presence of Ru^{3+} . Four degraded products of linezolid were identified with the help of HR-MS data. Based on kinetic and HR-MS data, a plausible catalytic mechanism was proposed. In this mechanism, Ru^{3+} acts as an electron shuttle and was oxidized by Mn^{7+} to the higher oxidation states of ruthenium such as Ru^{6+} and Ru^{7+} . Activation parameters were determined and discussed.

Keywords: Ru^{3+} Catalysis, Linezolid, Permanganate, Kinetics, Water treatment, Degradation.

INTRODUCTION

For more than three decades, pharmaceutical compounds have been emerging as harmful contaminants, which are detected in drinking water as well as wastewater across the world. It has been reported by the local and worldwide bodies that there is a significant concern of pharmaceutical compounds in the aquatic environment [1]. In the aquatic environment, the presence of antibacterial residues raises concern due to their ability to promote the growth of antibacterial resistant organisms, which pose health hazards to human beings. Understanding the transformation of antibacterial in the aquatic environment is critical to evaluate the hazards associated with these emerging contaminants [2].

Potassium permanganate (Mn^{7+}) is a potent oxidizing agent and it does not produce environmentally hazardous by-products. Potassium permanganate is applied mainly to eliminate colour and odour as well as to control microbial growth in water treatment plants. Permanganate may also help in reducing the production of trihalomethanes and other disinfection by-products [3]. Permanganate is the most capable and potent oxidizing agent in both acidic as well as in alkaline medium [4-6].

Linezolid (LNZ) is an oxazolidinone class of antibacterial and has 1,3-oxazolidinone moiety containing acetamide subgroup at 5th methyl group position (Fig. 1). Linezolid has been used extensively for many years to cure infections [7]. It shows weak basic properties (pKa 1.8) and slightly soluble in water at pH values between 5.0 and 9.0 [8,9]. Unnecessary or excessive use of any antibiotic can lead to its decreased effectiveness.

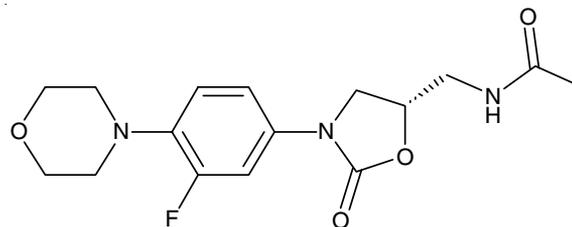


Fig. 1. Structure of linezolid

Now-a-days, utilization of transition metals has attracted significant attention as catalyst in various oxidation reduction reactions [10]. Ruthenium(III) $^{3+}$ played a vital role as an efficient catalyst due to its catalytic activity in the redox reactions

involving organic as well as inorganic compounds [11,12]. Oxidation-reduction reactions involving Ru^{3+} catalysis are very complicated because Ru^{3+} forms complex and oxidizes into various oxidation states during the reactions [13].

There is no information available in the literature on the degradation of linezolid by Mn^{7+} in the presence of Ru^{3+} catalyst and its catalytic mechanism. It is noticed that a small amount of Ru^{3+} is sufficient to catalyze the oxidative degradation of linezolid with Mn^{7+} at environmentally relevant pH (6.0-9.0). Such studies are of significance in understanding the mechanistic profile of linezolid in redox reactions and provide insight into the interaction of metal ions with the substrate and its mode of action in biological systems. Thus, the current study is taken up to study the redox chemistry involving linezolid, permanganate and Ru^{3+} , to analyze the products by characterization of samples, to propose a plausible mechanism, to deduce rate law and to evaluate thermodynamic parameters.

EXPERIMENTAL

All the chemicals used in this study are of AR grade. A requisite quantity of linezolid (Dr. Reddy Laboratories) sample was used to prepare a linezolid stock solution. The suitable quantity of KMnO_4 crystals (Merck) were dissolved to prepare a stock solution and standardized using oxalic acid as described in the literature [14]. In order to maintain the constant pH of the reaction mixture, 0.02 mol dm^{-3} acetate (pH 3-5), phosphate (pH 6.0-7.0) and borate buffers (pH 8.0-9.0) were used during experiments conducted in reagent water system. Double distilled water was added to prepare stock solutions of different reagents. The suitable quantity of RuCl_3 (S.D. Fine Chem.) was dissolved in 0.20 mol dm^{-3} HCl to prepare a required concentration of standard stock solution.

UV-Vis Spectrophotometer (A CARY 50 Bio, Varian BV, The Netherlands) with temperature controller was used for kinetic measurements. HPLC system (Shimadzu prominence) and Thermo Scientific Q Exactive High Resolution Mass Spectrophotometer (HR-MS) were used for product analysis. Column-Thermo Scientific Hypersil Gold C_{18} (150 \times 4.6 mm⁸ μm) was used. A pH meter (Elico, model LI 120) was used to measure pH during an experimental study.

Kinetic measurements: Pseudo first-order conditions were maintained to study the oxidative degradation of linezolid by Mn^{7+} , where [LNZ] was kept ten-fold excess over $[\text{Mn}^{7+}]$ at 25 ± 0.2 °C. The solutions of permanganate, linezolid and buffer were kept in a thermostat separately to attain constant temperature and these reagents were added to trigger the redox reaction. The decrease in the concentration of Mn^{7+} during the reaction was monitored at $\lambda_{\text{max}} = 526$ nm as a function of time. The application of Beer's law to permanganate at 526 nm is verified,

giving $\epsilon = 2283 \pm 20$ $\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$ (literature $\epsilon = 2200$ $\text{dm}^3 \text{mol}^{-1} \text{cm}^{-1}$). It was confirmed that there was no significant interference from other species present in the reaction mixture at $\lambda_{\text{max}} 526$ nm [15]. From the plots of log (absorbance) versus time, k_{obs} i.e. pseudo-first order rate constants were calculated. The plots were obtained linear for the completion of reaction almost up to 80 %. The rate constants were reproducible within an error margin of ± 8 %. Analysis of the products of reaction was carried out by HPLC system of Shimadzu Prominence and Thermo Scientific Q Exactive HR-MS.

Product identification method: In order to achieve the initial concentration of 400 mg dm^{-3} , linezolid was mixed with 0.02 mol dm^{-3} phosphate buffer of pH = 6 and permanganate solution of higher concentration compared to linezolid was mixed to set up the reaction. This was placed for the period of 24 h to complete the reaction. Subsequently, the products of the reaction were analyzed by using Thermo Scientific Q Exactive HR-MS with a column Thermo Scientific Hypersil Gold C_{18} having diameter 150 mm \times 4.6 mm and particle size 8 μm . By keeping proportion of acetonitrile and double distilled water as 50:50 and pressure 33.2 bar with flow rate 500.0 $\mu\text{L}/\text{min}$, HR-MS instrumental analysis has done from the range of 100-800 m/z by using ESI⁺. The proposed structures of the reaction products were identified based on the observed peaks of HR-MS spectra as shown in Fig. 2 and are listed in Table-1.

RESULTS AND DISCUSSION

Reaction orders: The oxidative degradation of linezolid by permanganate for uncatalyzed reaction progresses with a considerable rate. It was experimentally found that the orders with respect to Mn^{7+} and linezolid are unity and fractional respectively. Hence it can be mathematically expressed as:

$$\text{Rate} = \frac{-d[\text{MnO}_4^-]}{dt} = k_U [\text{Mn}^{7+}]^1 [\text{LNZ}]^{0.61} \quad (1)$$

In the above mentioned eqn. 1, k_U is the rate constant for uncatalyzed reaction between linezolid and permanganate at environmentally relevant pH. The catalytic oxidative degradation of linezolid by Mn^{7+} in the presence of Ru^{3+} shows a parallel pathway with inputs both from uncatalyzed and Ru^{3+} catalyzed reactions (eqn. 2-8). Therefore, overall rate constant (k_o) can be written as follow:

$$k_o = k_U + k_C \quad (2)$$

Here, k_U is the rate constant for the oxidative degradation of linezolid by Mn^{7+} without catalyst. k_C is the rate constant for the oxidative degradation of linezolid by Mn^{7+} in the presence of Ru^{3+} catalyst. Therefore;

$$k_C = k_o - k_U \quad (3)$$

TABLE-1
IDENTIFIED PRODUCTS OF OXIDATIVE DEGRADATION OF ANTIBACTERIAL
LNZ BY Mn^{7+} AT ENVIRONMENTALLY RELEVANT pH by HR-MS ANALYSIS

LNZ products	Retention time (min)	Measured molecular ion peak (M + H ⁺)	Theoretical mass of products (Da)	m.f.	(Measured mass – Theoretical mass)	Degradation site moiety
LNZ_P1	3.29	159.07	158 (Major Product)	$\text{C}_6\text{H}_{10}\text{N}_2\text{O}_3$	+1.07	Morpholine
LNZ_P2	3.29	181.05	180	$\text{C}_{10}\text{H}_{11}\text{NOF}$	+1.05	Oxazolidinone
LNZ_P3	3.29	197.03	196	$\text{C}_9\text{H}_5\text{NO}_2\text{F}$	+1.03	Oxazolidinone and phenyl
LNZ_P4	3.73	352.12	351	$\text{C}_{16}\text{H}_{18}\text{N}_3\text{O}_5\text{F}$	+1.12	Morpholine

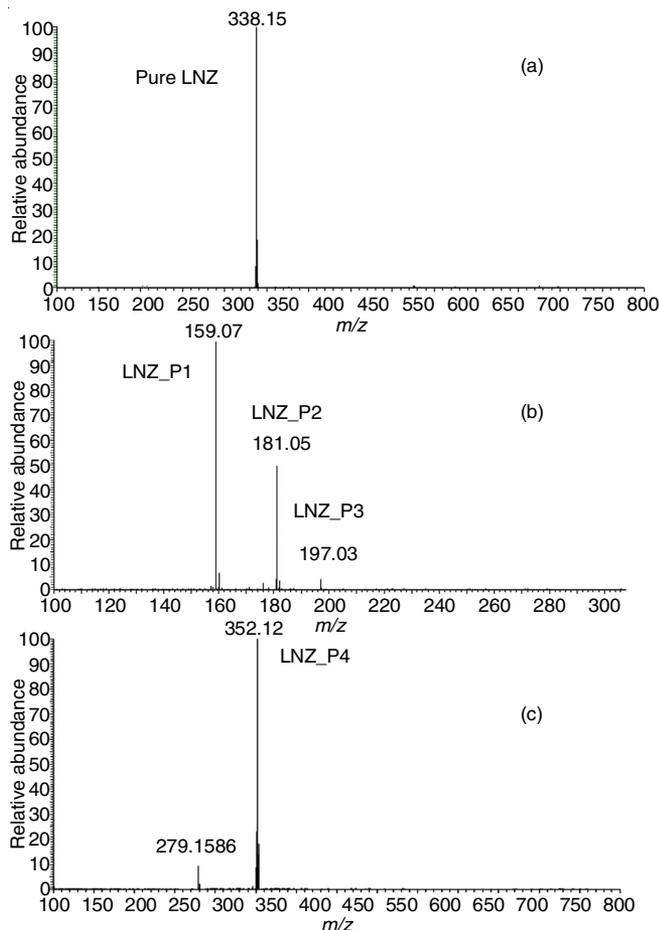
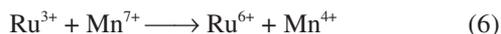


Fig. 2. HR-MS spectra of (a) pure LNZ with its molecular ion peak (M + H)⁺ m/z at 338.15. (b) Molecular ion peaks (M+H)⁺ m/z at 159.07, 181.05 and 197.03 for degraded products LNZ_P1, LNZ_P2 and LNZ_P3 respectively. (c) Molecular ion peak (M+H)⁺ m/z at 352.12 for product LNZ_P4



By using slopes of plots of $\log k_U$ versus $\log(\text{conc.})$ of the oxidative degradation of linezolid without catalyst, reaction orders have been calculated for linezolid and Mn^{7+} . It was found first order with respect to Mn^{7+} and fractional order with respect to linezolid. Similarly, by using slopes of the plots of $\log k_{\text{obs}}$ vs. $\log(\text{conc.})$ of oxidative degradation of linezolid with Ru^{3+} catalytic reaction, orders have been calculated for linezolid, Mn^{7+} and Ru^{3+} catalyst. The reaction was found first order with respect each Mn^{7+} , linezolid and Ru^{3+} in catalyzed reaction. From the kinetic studies of Ru^{3+} catalytic permanganate oxidative degradation of linezolid at environmentally relevant pH, the rate of the oxidative degradation reaction by using rate law can be written as follows:

$$\text{Rate} = \frac{-d[\text{MnO}_4^-]}{dt} = k_o[\text{Mn}^{7+}][\text{LNZ}] \quad (9)$$

$$\text{Rate} = \frac{-d[\text{MnO}_4^-]}{dt} = (k_U + k_C)[\text{Mn}^{7+}][\text{LNZ}] \quad (10)$$

Effect of concentration of permanganate: For uncatalyzed reaction, $[\text{Mn}^{7+}]$ varied from 2.5×10^{-5} mol dm^{-3} to 2.5×10^{-4} mol dm^{-3} by keeping the fixed $[\text{LNZ}] = 1 \times 10^{-3}$ mol dm^{-3} , $[\text{Buffer}] = 6 \times 10^{-3}$ mol dm^{-3} , ionic strength (I) = 0.02 mol dm^{-3} in order to maintain pH = 7 and constant ionic strength. Similarly, the concentration of oxidizing agent permanganate varied from 2.5×10^{-5} mol dm^{-3} to 2.5×10^{-4} mol dm^{-3} by keeping the fixed $[\text{LNZ}] = 1 \times 10^{-3}$ mol dm^{-3} , $[\text{Ru}^{3+}] = 3 \times 10^{-7}$ mol dm^{-3} and $[\text{Buffer}] = 6 \times 10^{-3}$ mol dm^{-3} , ionic strength (I) = 0.02 mol dm^{-3} in order to maintain pH = 7 and fixed ionic strength for Ru^{3+} catalyzed reaction. The plots of $\log \text{abs}$ versus time are obtained straight line with slope for different initial $[\text{Mn}^{7+}]$, which shows that an experimental order was unity for $[\text{Mn}^{7+}]$ in both oxidative degradation reactions of linezolid by Mn^{7+} for uncatalyzed and catalyzed at environmentally relevant pH and 298 K.

Dependence of reaction rate on [LNZ]: Dependence of rate of the reaction on [LNZ] was investigated thoroughly at fixed $[\text{Mn}^{7+}] = 1 \times 10^{-4}$ mol dm^{-3} , $[\text{Ru}^{3+}] = 3 \times 10^{-7}$ mol dm^{-3} , $[\text{Buffer}] = 6 \times 10^{-3}$ mol dm^{-3} , ionic strength (I) = 0.02 mol dm^{-3} at environmentally relevant pH and temperature 298 K. [LNZ] was varied from 5×10^{-4} mol dm^{-3} to 3.0×10^{-3} mol dm^{-3} for oxidative degradation of linezolid by Mn^{7+} in both uncatalyzed and Ru^{3+} catalyzed reactions at 298 K. It is observed that k_{obs} increases with increase in [LNZ]. From the plot of $\log k_{\text{obs}}$ versus $\log [\text{LNZ}]$ for uncatalyzed reaction, the order for linezolid is found to be fractional (0.61). From the plot of $\log k_{\text{obs}}$ versus $\log [\text{LNZ}]$ for catalyzed reaction, the order for linezolid is found to be almost unity (0.91).

Test for free radical involvement: The reaction mixtures of uncatalyzed and catalyzed reactions were mixed with required quantity of acrylonitrile monomer and placed for 5 h. Methyl alcohol was used for the dilution of linezolid and permanganate mixture which didn't form any insoluble compound. This clearly indicates that no free radical was involved in both these reactions [16].

Dependence of rate of reaction on varying ionic strength and solvent polarity: Dependence of rate of the reaction on varying ionic strength was investigated by changing [buffer] of pH = 7 starting with 0.002 mol dm^{-3} to 0.012 mol dm^{-3} at 298 K. No significant impact of ionic strength on the reaction rate is observed for uncatalyzed and Ru^{3+} catalyzed reactions at environmentally relevant pH and temperature 298 K.

Dependence of rate of reaction on solvent polarity was investigated for the variation of a mixture of tertiary butanol and water for uncatalyzed and Ru^{3+} catalyzed reactions by maintaining all other reaction conditions constant, $[\text{MnO}_4^-] = 1 \times 10^{-4}$ mol dm^{-3} , $[\text{LNZ}] = 1 \times 10^{-3}$ mol dm^{-3} , $[\text{Ru}^{3+}] = 3 \times 10^{-7}$ mol dm^{-3} , $[\text{Buffer}] = 6 \times 10^{-3}$ mol dm^{-3} , ionic strength (I) = 0.02 mol dm^{-3} at environmentally relevant pH and temperature 298 K. It was found that as the volume of *tert*-butanol increases then the rate of reaction decreases. It means that increase in the dielectric constant of reaction medium decreases the reaction rate of Ru^{3+} catalytic oxidative degradation reactions of linezolid by permanganate at environmentally relevant pH and temperature 298 K as shown in Fig. 3. There is no interference of solvent

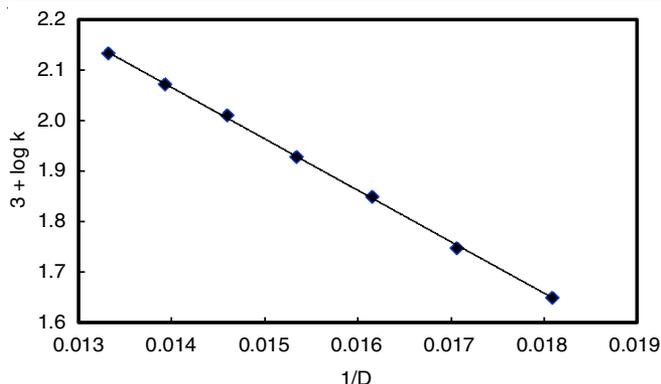


Fig. 3. Solvent polarity effect on Ru^{3+} catalytic permanganate oxidative degradation of LNZ at environmentally relevant pH 7 (temperature 298 K). $[\text{Mn}^{7+}] = 1 \times 10^{-4} \text{ mol dm}^{-3}$, $[\text{LNZ}] = 1 \times 10^{-3} \text{ mol dm}^{-3}$, $[\text{Ru}^{3+}] = 3 \times 10^{-7} \text{ mol dm}^{-3}$, $[\text{Buffer}] = 6 \times 10^{-3} \text{ mol dm}^{-3}$ and ionic strength (I) = 0.02 mol dm^{-3}

with the oxidant under the experimental conditions. The plot of $\log k_{\text{obs}}$ versus $1/D$ was found linear with a negative slope as it was also reported in previous investigation [4].

Effect of variation of $[\text{Ru}^{3+}]$: Variation in $[\text{Ru}^{3+}]$ from 5.0×10^{-8} to $5.0 \times 10^{-7} \text{ mol dm}^{-3}$ was investigated for Ru^{3+} catalytic oxidative degradation reactions of linezolid by permanganate at environmentally relevant pH and temperature 298 K by keeping other reaction conditions constant such as $[\text{MnO}_4^-] = 1 \times 10^{-4} \text{ mol dm}^{-3}$, $[\text{LNZ}] = 1 \times 10^{-3} \text{ mol dm}^{-3}$, $[\text{Buffer}] = 6 \times 10^{-3} \text{ mol dm}^{-3}$ and ionic strength (I) = 0.02 mol dm^{-3} . It is observed that the rate of reaction increases with increase in $[\text{Ru}^{3+}]$. From the straight line plot of $\log K_{\text{obs}}$ versus $\log [\text{Ru}^{3+}]$, it is observed that order with respect to $[\text{Ru}^{3+}]$ is almost unity (0.88) ($R^2 > 0.999$) as shown in Fig. 4.

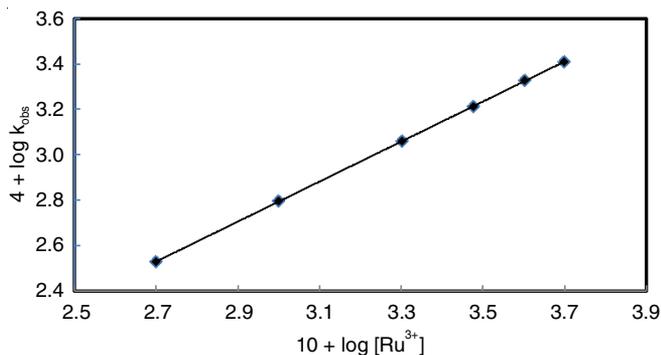


Fig. 4. Effect of Ru^{3+} catalyst concentrations on oxidative degradation of LNZ by Mn^{7+} at environmentally relevant pH 7 (temperature 298 K). $[\text{Ru}^{3+}] = 5 \times 10^{-8} \text{ mol dm}^{-3}$ to $5 \times 10^{-7} \text{ mol dm}^{-3}$, $[\text{Mn}^{7+}] = 1 \times 10^{-4} \text{ mol dm}^{-3}$, $[\text{LNZ}] = 1 \times 10^{-3} \text{ mol dm}^{-3}$, $[\text{Buffer}] = 6 \times 10^{-3} \text{ mol dm}^{-3}$ and ionic strength (I) = 0.02 mol dm^{-3}

Catalytic activity: According to Moelwyn-Hughes [17] reactions with and without catalyst proceed simultaneously for which

$$k_0 = k_U + K_C^* [\text{Ru}^{3+}]^m \quad (11)$$

In this above equation, k_U and k_0 indicate the observed pseudo first order rate constant for reactions without catalyst and with Ru^{3+} catalyst, respectively. K_C represents catalytic constant while 'm' represents order with respect to catalyst Ru^{3+} . Values of 'm' were considered to be unity for the standard run. By using an equation, catalytic constant (K_C^*) is evaluated.

$$K_C^* = \frac{[k_0 - k_U]}{[\text{Ru}^{3+}]^m} = \frac{k_C}{[\text{Ru}^{3+}]^m} \quad (\text{where } k_0 - k_U = k_C) \quad (12)$$

$$k_C = K_C^* \times [\text{Ru}^{3+}]^m \quad (13)$$

The value of catalytic constant K_C^* can be calculated by using the eqn. 12 as follow:

$$K_C^* = (9.06 \times 10^{-2} - 5.04 \times 10^{-3}) / (3 \times 10^{-7})$$

$$K_C^* = 2.852 \times 10^5$$

Taking logarithm on both the sides of eqn. 13, we get

$$\ln k_C = \ln K_C^* + m \ln [\text{Ru}^{3+}] \quad (14)$$

The slope plot of $\ln k_C$ vs. $\ln [\text{Ru}^{3+}]$ shows that the reaction order 'm' was 1.0 approximately. The K_C^* is an intercept of this plot. Hence the above equation becomes,

$$\text{Rate} = \frac{-d[\text{MnO}_4^-]}{dt} = (k_U + k_C^* [\text{Ru}^{3+}]^1) [\text{Mn}^{7+}]^1 [\text{LNZ}]^1 \quad (15)$$

Effect of pH: The effect of pH was investigated thoroughly by varying $[\text{LNZ}]$ from $5 \times 10^{-4} \text{ mol dm}^{-3}$ to $3.0 \times 10^{-3} \text{ mol dm}^{-3}$ at different pH maintaining other parameters fixed for uncatalyzed and Ru^{3+} catalyzed reactions. The reaction rate found to be decreased with increase in pH. k_U'' and k_C'' are apparent second order rate constants values for uncatalyzed and catalyzed reactions, respectively as shown in Fig. 5 and listed in Table-2. The effect of pH has shown that the second order rate constant is higher in acidic condition and lower in alkaline condition. The rate of the reaction at pH = 7 shows that removal of linezolid can be carried out at environmentally relevant pH.

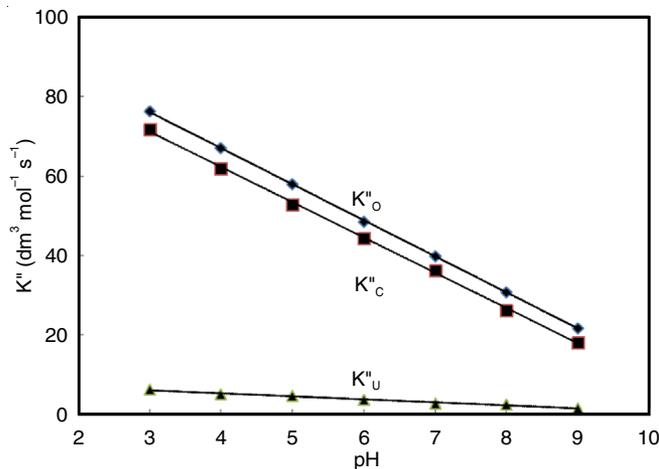


Fig. 5. pH dependent apparent second order rate constants of uncatalyzed and Ru^{3+} catalyzed reactions for permanganate oxidative degradation of LNZ at different pH from 3.0 to 9.0 (temperature 298 K). $[\text{Mn}^{7+}] = 1 \times 10^{-4} \text{ mol dm}^{-3}$, $[\text{LNZ}] = 1 \times 10^{-3} \text{ mol dm}^{-3}$, $[\text{Ru}^{3+}] = 3 \times 10^{-7} \text{ mol dm}^{-3}$, $[\text{Buffer}] = 6 \times 10^{-3} \text{ mol dm}^{-3}$ and ionic strength (I) = 0.02 mol dm^{-3}

Effect of initially added product on the rate of reaction:

Reaction mixtures of both catalyzed and uncatalyzed reactions were spiked with manganese dioxide. It was found that the effect of addition of manganese dioxide is negligible for uncatalyzed and Ru^{3+} catalyzed reactions at environmentally relevant pH because increase of pH of the reaction mixture decreases the catalytic potential of manganese dioxide considerably and hence there was no catalytic effect was observed

TABLE-2

pH DEPENDENT APPARENT SECOND ORDER RATE CONSTANT FOR THE EFFECT OF VARIATION OF pH ON THE UNCATALYZED AND Ru³⁺ CATALYZED OXIDATIVE DEGRADATION OF LINEZOLID BY Mn⁷⁺ AT DIFFERENT pH FROM 3.0 TO 9.0 (TEMPERATURE 298 K). [Mn⁷⁺] = 1 × 10⁻⁴ mol dm⁻³, [LNZ] = 1 × 10⁻³ mol dm⁻³, [Ru³⁺] = 3 × 10⁻⁷ mol dm⁻³, [Buffer] = 6 × 10⁻³ mol dm⁻³ AND IONIC STRENGTH (I) = 0.02 mol dm⁻³

pH	k _u [*]	k _o [*]	k _c [*]
3.0	6.32	78.44	72.12
4.0	5.18	66.76	61.58
5.0	4.73	57.56	52.83
6.0	3.73	48.49	44.76
7.0	2.83	38.19	35.36
8.0	2.62	27.53	25.37
9.0	1.56	16.99	13.98

by manganese dioxide at environmentally relevant pH. This was also reported in earlier investigation [13].

Temperature effect on reaction rate: The rate constants were determined for both uncatalyzed and Ru³⁺ catalyzed reactions at four different temperatures (283, 288, 296 and 299 K) by varying [LNZ], while freezing other experimental conditions such as [Mn⁷⁺] = 1 × 10⁻⁴ mol dm⁻³, [Ru³⁺] = 3 × 10⁻⁷ mol dm⁻³, [Buffer] = 6 × 10⁻³ mol dm⁻³ and ionic strength (I) = 0.02 mol dm⁻³. Higher rate constants were observed with increase in temperature of the reaction. Activation parameters *i.e.* E_a, ΔH[#], ΔG[#] and ΔS[#] were calculated from the Arrhenius plot log k versus 1/T (R² > 0.99) as shown in Fig. 6 and are listed in Table-3.

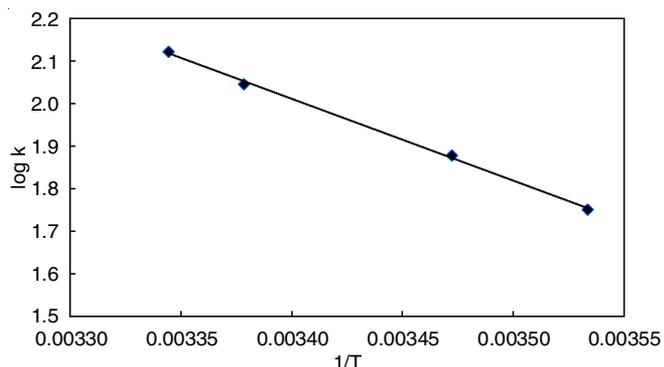


Fig. 6. Arrhenius plot log k versus 1/T for four different temperatures by varying [LNZ] from 5 × 10⁻⁴ to 3 × 10⁻³ mol dm⁻³, while freezing other experimental conditions such as [Mn⁷⁺] = 1 × 10⁻⁴ mol dm⁻³, [Ru³⁺] = 3 × 10⁻⁷ mol dm⁻³, [Buffer] = 6 × 10⁻³ mol dm⁻³ and ionic strength (I) = 0.02 mol dm⁻³

The catalytic permanganate oxidative degradation of linezolid at environmentally relevant pH shows order unity for Mn⁷⁺, Ru³⁺ and linezolid. The effect of pH on the oxidative degradation of linezolid by Mn⁷⁺ for its removal was studied thoroughly from the pH 3.0-9.0 for uncatalyzed and Ru³⁺ catal-

yzed reactions. As the pH increases from 3.0-9.0, the removal of linezolid decreases due to decrease in the concentration of H⁺ ions and also decrease in the oxidation potential of permanganate. The second order rate constants for oxidative degradation of linezolid by Mn⁷⁺ in the presence of Ru³⁺ is decreasing from pH 3.0-9.0. Ru³⁺ increases the removal of linezolid at the lower pH. It indicates that at the lower values of pH, Ru³⁺ gets oxidized to the higher oxidation states Ru⁷⁺ and Ru⁶⁺ by Mn⁷⁺ in the acidic medium while Mn⁷⁺ get reduced to Mn⁴⁺ ion [13,18]. The oxidized forms of ruthenium (Ru⁷⁺ and Ru⁶⁺) which are formed *in situ* then degrade linezolid rapidly and get converted into the original form Ru³⁺.

In alkaline conditions, the rate of oxidative degradation of linezolid was found low. A small amount of oxidized forms of ruthenium were formed at alkaline conditions due to the low oxidation potential of permanganate at the higher alkaline pH. Ru (oxidized) forms are acting as a co-oxidant to accelerate the rate of the removal of linezolid. This was also reported by the investigation of removal of aniline at environmentally relevant pH [13].

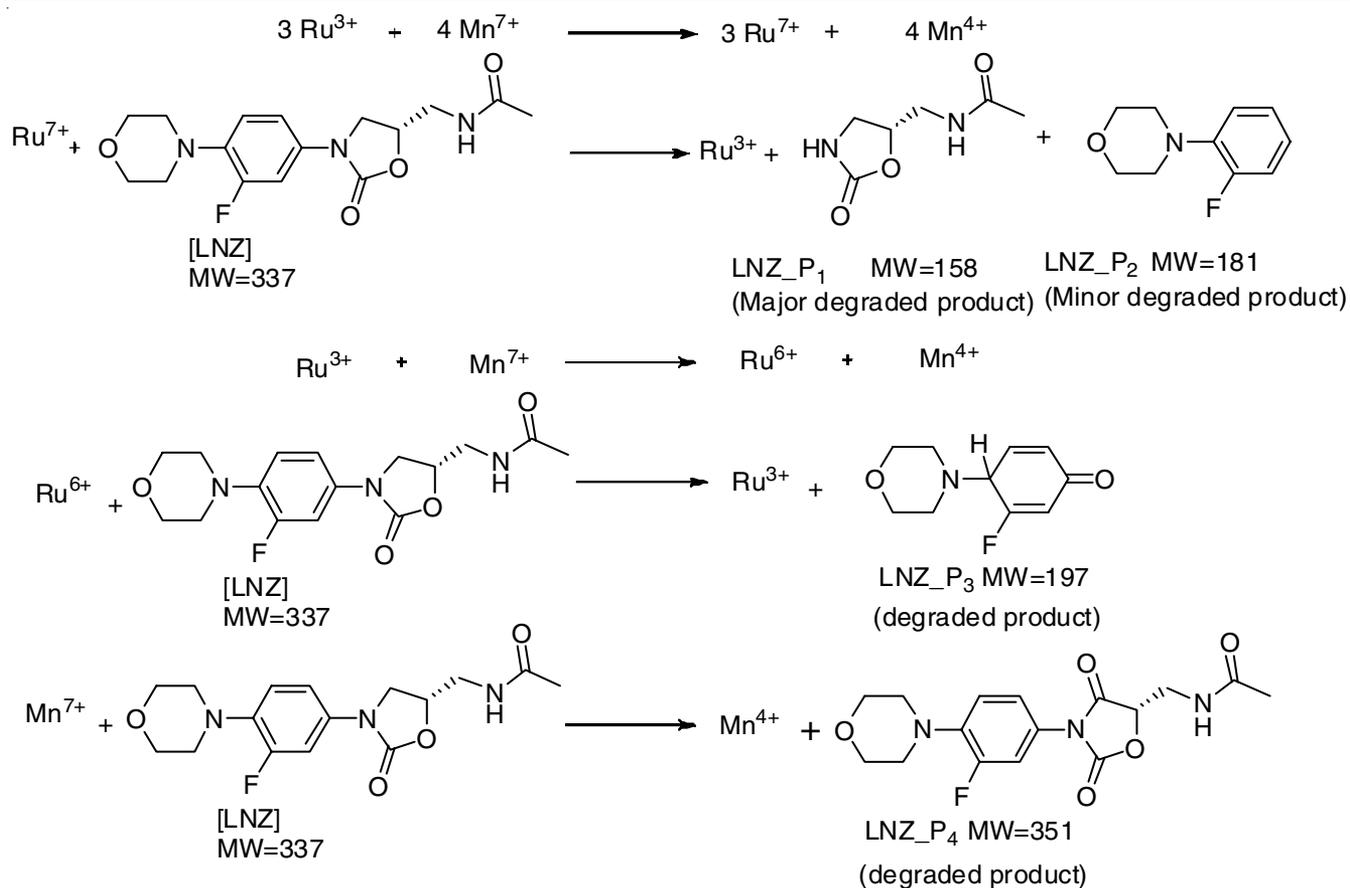
Identification of four products of oxidative degradation of linezolid by permanganate was done by using HR-MS spectra. LNZ_P1 is the first product identified as protonated peak at *m/z* 159.07, which is due to oxazolidinone of acetamide from fragmentation of linezolid. This is a stable phenyl carbocation and N-(2-oxo-oxazolidin-5-ylmethyl)acetamide (*m/z* 158). The second product LNZ_P2 identified as protonated peak at *m/z* 181.05 is due to fluorophenyl morpholine from the fragmentation of linezolid molecule. The product LNZ_P2 is 4-(2-fluorophenyl)morpholine (*m/z* 181). The third product LNZ_P3 identified as protonated peak at *m/z* 197.03, which is due to further oxidation of fluorophenyl morpholine into fluoromorpholine phenol. The product LNZ_P3 is 3-fluoro-4-morpholin-4-yl-cyclohexa-2, 5-dienone (*m/z* 197). The fourth product LNZ_P4 identified as protonated peak at *m/z* 352.12, which is due to direct oxidation of linezolid molecule to N-{3-[3-fluoro-4-(2-oxo-morpholin-4-yl)phenyl]-2-oxo-oxazolidin-5-yl-methyl}acetamide.

Based on kinetic data and HR-MS spectra, a plausible mechanism is proposed as shown in **Scheme-I** and orders with respect to [Mn⁷⁺], [Ru³⁺] and [LNZ] were taken into account. Various degraded products formed in the permanganate oxidative degradation of linezolid in uncatalyzed and Ru³⁺ catalyzed reactions at environmentally relevant pH were same and indicate the behaviour of ruthenium catalyst similar with Mn⁷⁺ ion [19]. The proposed catalytic mechanism for the oxidative degradation of linezolid by Mn⁷⁺ in the environmentally relevant pH (**Scheme-I**) shows similarity with the previous investigations of the oxidative degradation by permanganate in the presence of ruthenium catalyst [18]. In this mechanism,

TABLE-3

CALCULATION OF ACTIVATION PARAMETERS AND THERMODYNAMIC QUANTITIES AT DIFFERENT TEMPERATURES

Temperature effect on the rate of the reaction			Activation parameters		
Temp. (K)	10 ³ k _u (s ⁻¹)	10 ² k _c (s ⁻¹)	Activation parameters	Values uncatalyzed	Values Ru ³⁺ catalyzed
283	3.96	11.2	E _a (kJ mol ⁻¹)	39.08 ± 2.02	33.88 ± 2.00
288	6.96	17.6	ΔH [#] (kJ mol ⁻¹)	36.66 ± 2.00	31.46 ± 1.50
296	8.68	20.88	ΔS [#] (JK ⁻¹ mol ⁻¹)	-160.06 ± 14.20	-150.81 ± 13.20
299	10.56	26.89	ΔG [#] (kJ mol ⁻¹)	83.32 ± 7.40	75.42 ± 6.30



Scheme-I: Proposed mechanism for catalytic degradation of LNZ by Mn^{7+} at environmentally relevant pH

there is an interaction between Mn^{7+} and Ru^{3+} . Mn^{7+} oxidizes Ru^{3+} to Ru^{6+} and Ru^{7+} while Mn^{7+} was reduced to Mn^{4+} ion [18]. K_2RuO_4 was synthesized from KRuO_4 as per the method reported in literature [19]. The kinetics experiments were carried out in the presence of Ru^{3+} , Ru^{7+} and Ru^{6+} separately to study the effect of these catalysts. The kinetic data shows that Ru^{7+} is a better oxidizing agent than Ru^{3+} and also Ru^{6+} . Ru^{6+} was synthesized in the laboratory from KRuO_4 was unstable due to its fast conversion into $\text{Ru}(\text{OH})_4$. But even an extremely small amount of Ru^{6+} also oxidized linezolid and reduced to Ru^{3+} . In the next step, Mn^{7+} oxidizes Ru^{6+} to a more stable oxidant Ru^{7+} . Then Mn^{7+} oxidized linezolid and it was reduced to Mn^{4+} . In this Ru^{3+} permanganate catalytic mechanism of

linezolid at environmentally relevant pH, the four degraded products of linezolid are identified as LNZ_P1, LNZ_P2, LNZ_P3 and LNZ_P4.

In this catalytic mechanism, Ru^{7+} is the major active species of ruthenium which speedily oxidizes linezolid into different byproducts. This mechanism indicates that Ru^{3+} played a vital role of electron shuttle in the removal of linezolid by its degradation at pH 7. The catalytic role of Ru^{3+} in the oxidative degradation of linezolid by permanganate is shown in Fig. 7. Similar catalytic mechanism was also reported in earlier investigation [20]. The experimental results are explained in the proposed **Scheme-I**. Ru^{3+} catalyzed oxidative degradation of linezolid by heptavalent manganese results can be elucidated as per the

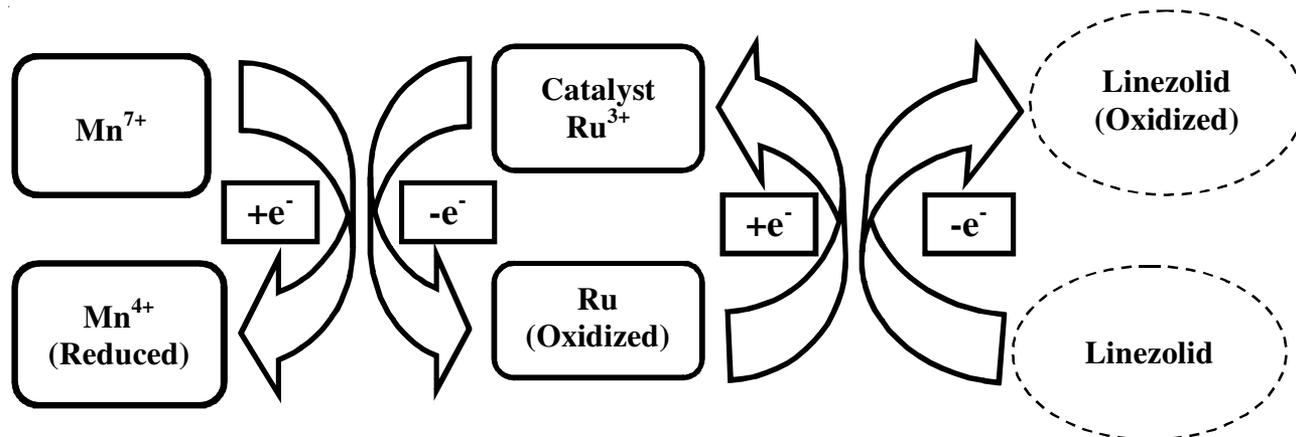


Fig. 7. Catalytic role of Ru^{3+} in the permanganate oxidation of LNZ at environmentally relevant pH

plausible mechanism. E_a was computed by using the straight line nature of Arrhenius plot between $\log k_{\text{obs}}$ vs. $1/T$. By using E_a , values of ΔH^\ddagger , ΔS^\ddagger and ΔG^\ddagger are determined [21].

The negative value of ΔS^\ddagger indicates that the degraded product is more ordered and tightly bound as compared to reactants. On the other hand, positive values of ΔG^\ddagger and ΔH^\ddagger show solvated degraded products. E_a , ΔG^\ddagger and ΔS^\ddagger values shows that catalyst Ru^{3+} gets oxidized rapidly to Ru^{7+} by Mn^{7+} in comparison with other catalyst. The proposed catalytic mechanism for oxidative degradation of linezolid with permanganate shows consistency with the determined rate law (**Scheme-I**).

The determined values of ΔH^\ddagger , ΔS^\ddagger , ΔG^\ddagger and E_a for catalyst Ru^{3+} and without catalyst show the effect of catalyst on the rate of reaction. Mn^{7+} oxidizes Ru^{3+} to Ru^{7+} which reacts with linezolid to form degraded products that increases higher reducing property of linezolid as compared to uncatalyzed reaction. Ru^{3+} catalysis decreases E_a by modifying the path of reaction.

Negligible effect of ionic strength on Ru^{3+} catalyzed and uncatalyzed reactions of linezolid by permanganate described the reaction is between neutral and charged species or two neutral species [22]. The influence of solvent polarity shows that the oxidation of linezolid by permanganate reaction is between two dipoles which is explained by Amis [23].

Conclusion

The kinetic and mechanistic oxidative degradation of linezolid by Mn^{7+} without catalyst and in the presence of catalyst Ru^{3+} was studied first time. Linezolid has been used as a model pharmaceutical compound for the degradation of pharmaceutical waste. The second order rate constants for the oxidative degradation of linezolid at environmentally relevant pH indicate that the rate of reaction is 12 times faster in Ru^{3+} catalyzed reaction than uncatalyzed reaction. It becomes evident that the reaction medium plays a significant role during the uncatalyzed and Ru^{3+} catalyzed reaction. The net sequence explained is in agreement with products formed and proposed mechanism. The four degraded products formed after the degradation of linezolid were detected in both uncatalyzed and Ru^{3+} catalyzed reactions. Ru^{3+} catalytic degradation of linezolid by permanganate shows order unity with respect to $[\text{Ru}^{3+}]$, $[\text{Mn}^{7+}]$ and $[\text{LNZ}]$. The proposed mechanism (**Scheme-I**) describes experimental results. The catalytic mechanism was proposed in which Ru^{3+} acts as an electron shuttle and oxidized by Mn^{7+} to the higher oxidation states of ruthenium (Ru^{6+} and Ru^{7+}). Ru^{6+} and Ru^{7+} acts as co-oxidants and degrades linezolid. This kinetic and mechanistic investigation clearly shows that Ru^{3+} is a potent catalyst for oxidative degradation of linezolid by permanganate at environmentally relevant pH.

CONFLICT OF INTEREST

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

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