

## SPECTROSCOPIC INVESTIGATIONS OF PERMANGANATE OXIDATION OF METFORMIN HYDROCHLORIDE IN ALKALINE CONDITION

*Ravindra K S, Vidyavati Shastry & Ramyashree H*

*Research Scholar, Department of chemistry, SEA College of Engineering and Technology, Bangalore, India*

### ABSTRACT

*Oxidation of Metformin hydrochloride (MET) by alkaline permanganate was calculated spectrophotometrically at 525nm. First order kinetics has been maintained during the reaction. The unit order dependence and fractional order which is observed with oxidant and drug respectively. The reaction between metformin hydrochloride and permanganate in presence of sodium hydroxide exhibits 1:1 stoichiometry. Product is identified by LCMS. The ionic strength and dielectric constant do not have significant effect on reaction. The activation parameters were determined at various temperatures. The reaction mechanism is proposed by experimental data. The experimental rate constants are in good agreement between experimental  $k$  values and theoretical  $k$  values.*

**KEYWORDS:** *Kinetics, Metformin Hydrochloride, Potassium Permanganate, Sodium Hydroxide, Potassium Chloride*

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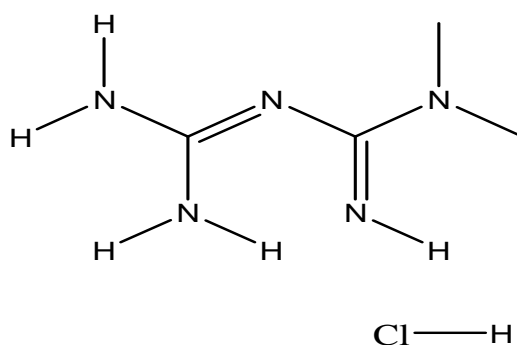
### Article History

**Received: 14 May 2020 / Revised: 18 May 2020 / Accepted: 27 May 2020**

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### INTRODUCTION

The Metformin is an oral antibiotic drug from the biguanide class<sup>[1]</sup>. It is used for the treatment of diabetes and is one of the most commonly used oral anti hyperglycemic medicament to treat type II diabetes, particularly in people who are heavyweight. It lowers the blood sugar and used as second line agent for infertility in those with polycystic ovary syndrome<sup>[2]</sup>. Overprotective high blood sugar helps prevent kidney damages, blindness, nerves problems, loss of limbs, and sexual functions problems. Its mechanism of action involves the suppression of endogenous glucose production, primarily by the liver. Whether the drug actually has an insulin sensitizing effect in peripheral tissues such as muscle and fat, remains somewhat controversial. Nonetheless, because insulin levels declining with metformin use, it has been termed an 'insulin sensitizer'. Metformin has also been shown to have several beneficial effects on cardiovascular risk factors and it is the only oral antihyperglycaemic agent thus far associated with decreased macrovascular outcomes in patients with diabetes<sup>[3]</sup>. Cardiovascular diseases, impaired glucose tolerances and the polycystic ovary symptoms are now recognised as complications of the insulin resistance syndrome, and there is growing interest in the management of this extraordinary common metabolic disorder. While diet and exercise remains the cornerstone of therapy for insulin resistances, pharmacological intervention is becoming an increasingly feasible option. Most common disadvantages of metformin is gastrointestinal irritations that include diarrheal, cramp, nausea, vomiting, and increased flatulence. The metformin has acid dissociation constant values ( $P^{ka}$ ) of 2.8 and 11.5<sup>[4]</sup>. Metformin hydrochloride (1, 1-dimethylbiguanide hydrochloride) is freely soluble in water. Chemical structure is given in Fig 1.



**Figure 1: Chemical Structure of Metformin Hydrochloride.**

Potassium permanganate is widely used as an oxidizing agent<sup>[5]</sup>. Among six oxidation states of manganese from +2 to +7, permanganate, Mn (VII) is the strong oxidation state in acid as well as basic media. The oxidation by permanganate ion finds extensive application in organic synthesis especially since the advent of phase transfer catalysis<sup>[6]</sup>. During oxidation by permanganate, it is evident that permanganate is reduced to various oxidation states in acidic, basic and neutral media<sup>[7]</sup>. Furthermore, the mechanism by which the multivalent oxidant oxidizes a substrate depends not only on the substrate but also on the medium used for the study. In strongly basic medium, the stable reduction product of permanganate ion is manganate ion<sup>[8]</sup>.

The permanganate ion reacts with alkaline medium to give  $[\text{MnO}_4 \text{ OH}]^{2-}$  species<sup>[9]</sup>. The objective of the current research was to study of oxidation of metformin hydrochloride by  $\text{KMnO}_4$  spectrophotometrically in basic medium.

## EXPERIMENTAL

### Result and Discussion

#### Materials

The Chemicals Metformin hydrochloride obtained from Naragund college of Pharmacy. Metformin hydrochloride was prepared by taking requisite amount of sample and dissolved in distilled water. Potassium permanganate, Sodium hydroxide, Potassium chloride was purchased from Nice chemicals and also prepared in double distilled water and standardized by standard methods<sup>[10]</sup>. All maintained chemicals and reagents were of analytical grade and used without any further purification. The absorbance of  $\text{KMnO}_4$  was recorded using systronic UV-vis Spectrophotometer at wavelength 525nm.

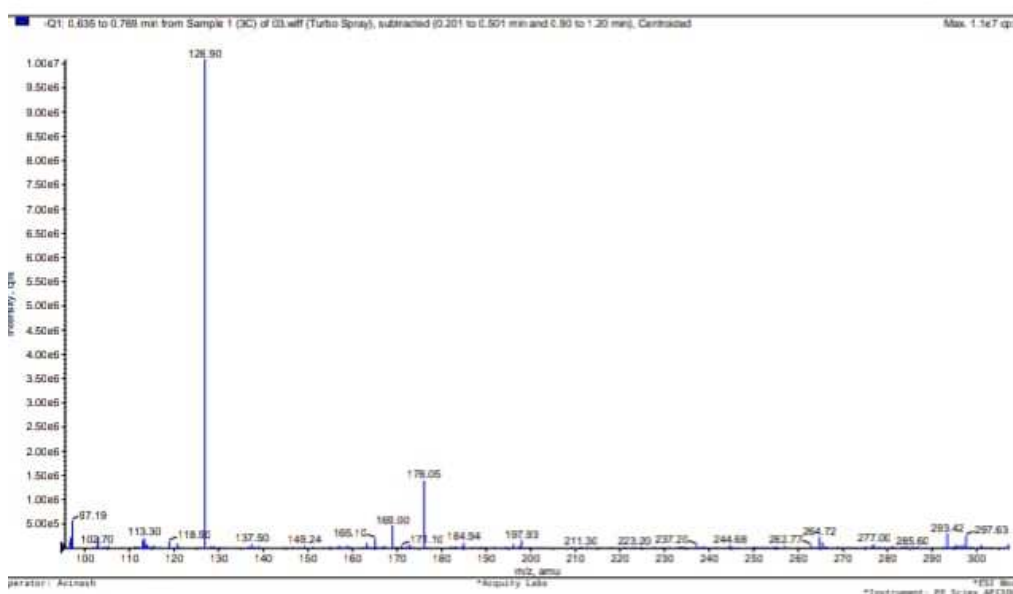
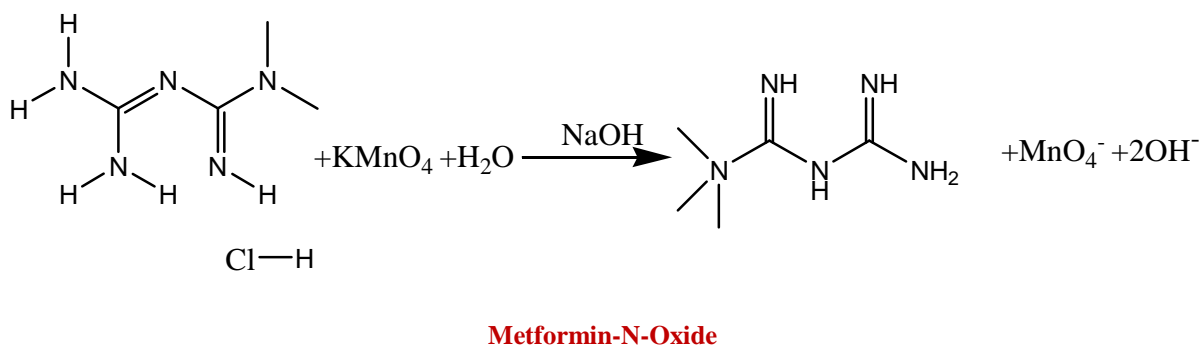
### KINETICS MEASUREMENTS

Kinetics measurements were performed under pseudo first order condition by taking  $[\text{Metformin Hydrochloride}] \gg [\text{Permanganate}]$  at constant ionic strength  $[2.5 \times 10^{-2}]$ . The reaction was initiated by mixing  $\text{MnO}_4^-$  and MET which also contained sodium hydroxide to maintain alkalinity. Reaction was followed by viewing the decrease in absorbance of  $\text{MnO}_4^-$ . Expansion of the reaction was observed spectrophotometrically by measuring the decrease in absorbance of  $\text{KMnO}_4$  at wavelength 525 nm. The pseudo first order rate constants were determined from  $\log [\text{absorbance}]$  v/s time. The plots were linear up to 80% of reaction and rate constants reproducible within  $\pm 5\%$  error.

## STIOCHIOMETRY

Stoichiometry was analysed periodically by spectrophotometric technique by keeping excess of permanganate than metformin hydrochloride at constant

$[\text{OH}^-]=5 \times 10^{-1}$ ,  $[\text{KCl}] = [2.5 \times 10^{-2}]$ . This reaction mixture was kept 24 hours at laboratory temperature and after the completion of reaction, excess of permanganate was measured using systronic UV-vis spectrophotometer at wavelength 525nm. The result indicates 1:1 stoichiometry between drug and oxidant. The oxidative product was found to be Metformin-N-oxide formed by reacting one mole of MET with one mole of permanganate. The products were analysed by LCMS spectra (Fig.2.) and is in good agreement with the results of product analysis. The peak is referred to Metformin- N-oxide.

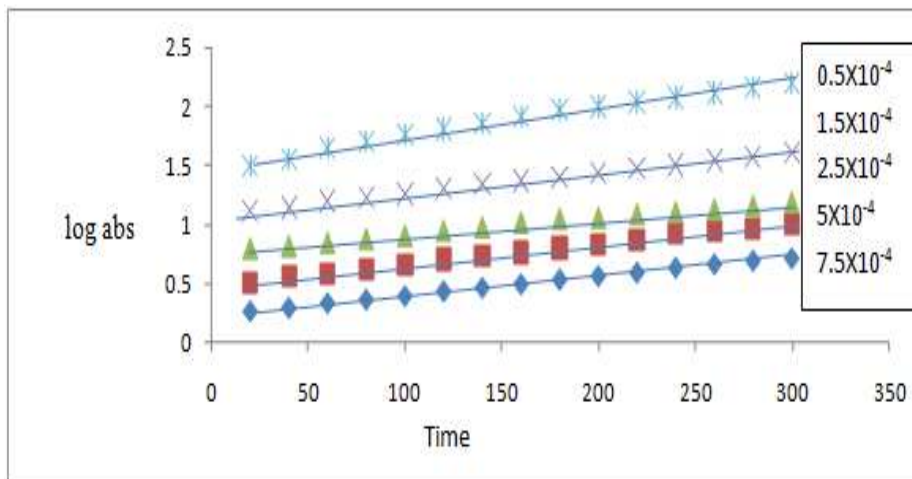


**Figure 2: LCMS Spectra of Oxidation of Product of Metformin Hydrochloride.**

## REACTION ORDER

### Effect of Potassium Permanganate

Variation of  $\text{KMnO}_4$  studied in the range  $0.5 \times 10^{-4}$  to  $7.5 \times 10^{-4}$  all other concentration Metformin hydrochloride  $[1 \times 10^{-3}]$ , Sodium hydroxide  $[1 \times 10^{-3}]$  and potassium chloride  $[1 \times 10^{-3}]$  are constant. It has been found that the plots log absorbance v/s time were linear up to 80% of the reaction which indicates the first order with respect to oxidant (Fig 3).



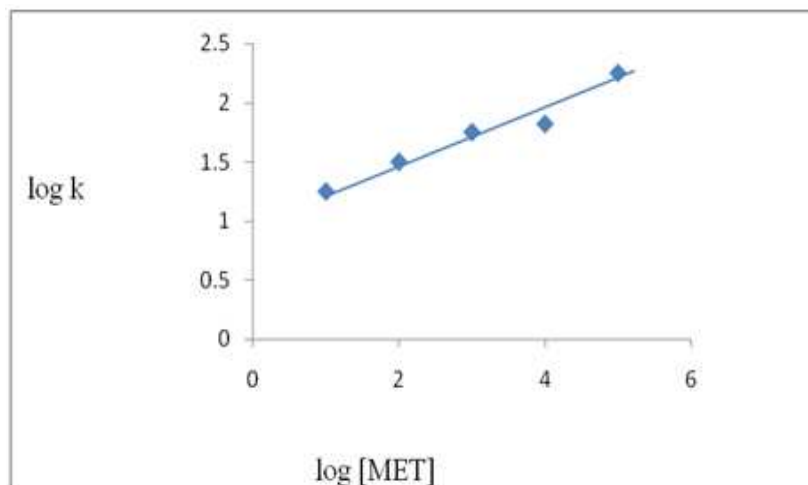
**Figure 3: A Graph of Log Absorbance Verses Time Shows First Order with Respect to Potassium Permanganate.**

### Effect of Variation of Metformin Hydrochloride

Variation of metformin hydrochloride studied in the range  $0.25 \times 10^{-3}$  to  $3 \times 10^{-3}$

While keeping all other reagents potassium permanganate [ $2.5 \times 10^{-4}$ ], potassium chloride

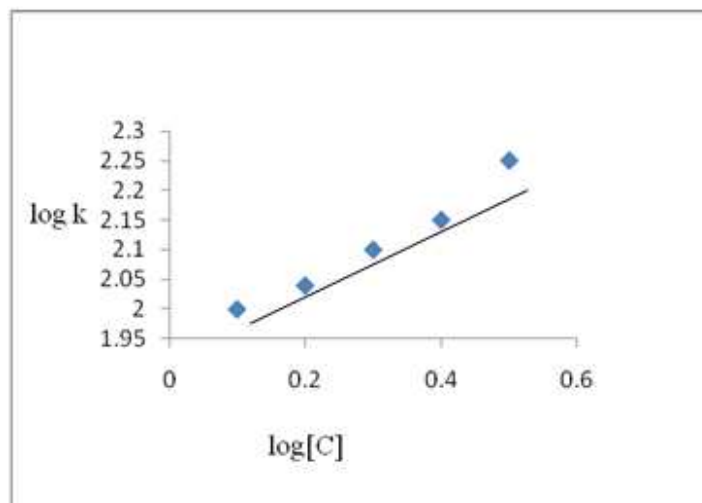
[ $2.5 \times 10^{-2}$ ] conditions were constant. A plot of  $\log k$  v/s time was drawn to calculate rate constant. A plot of  $\log k$  v/s [MET] were found to be linear with positive intercept confirming fractional order dependence with respect to metformin hydrochloride (Fig 4).



**Figure 4: A Graph of First Order Dependence with Respect to MET.**

### Effect of Sodium Hydroxide

NaOH varied from 1 to 10 mol  $\text{dm}^{-3}$  at fixed concentration of  $[\text{KMnO}_4] = [2.5 \times 10^{-4}]$ ,  $[\text{MET}] = [1.0 \times 10^{-3}]$ . An increase in concentration of alkali increases the rate.  $\log k$  v/s  $\log [\text{OH}^-]$  were found to be linear indicating fractional order with respect to  $\text{OH}^-$  (Fig 5).



**Figure 5: A Graph of Log[C] v/s Log [OH-].**

### Effect of Ionic Strength

The effect of Ionic Strength was studied by varying concentration of KCl from  $[1 \text{ to } 5 \times 10^{-2}]$  which concentration of all the reactant MET  $[1 \times 10^{-3}]$ ,  $\text{KMnO}_4 [2.5 \times 10^{-4}]$ ,  $\text{NaOH} [5 \times 10^{-1}]$  constant. It was observed that the Ionic strength did not show significant effect in the rate of the reaction.

### Effect of Added Salts

The effect of added salt was studied by varying concentration of NaCl,  $\text{AlCl}_3$ ,  $\text{CaCl}_2$ ,  $\text{Ca}(\text{NO}_3)_2$ , KBr. There was no regular trend observed for any of the added salts.

### Effect of Temperature

The effect of temperature was also studied at different temperatures like 298, 308, 312, 318 K fixed concentration of metformin hydrochloride, potassium permanganate, NaOH, KCl were at constant condition. The rate constant at different temperature  $K_{\text{obs}}$  were calculated. [Table I]. From linear Arrhenius plots of  $\log k$  v/s  $1/T$  (Fig.6) the activation parameters  $\Delta H^\ddagger$  ( $\text{KJmol}^{-1}$ ),  $\Delta S^\ddagger$  ( $\text{JK}^{-1}\text{mol}^{-1}$ ), &  $\Delta G^\ddagger$  ( $\text{KJmol}^{-1}$ ) were calculated and tabulated in Table II. Rate or rate constant is calculated at different temperature and is given in the Table I.

**Table 1: Rate Constant with Respect to Temperature**

Temperature	$K_{\text{obs}}$
298	0.0089
308	0.039
312	0.099
318	0.31

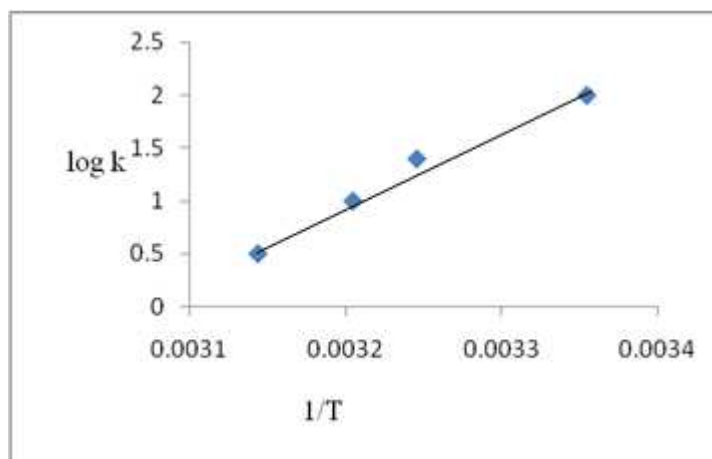


Figure 6: Arrhenius Plot of Log k v/s 1/T at Different Temperature.

Table 2: Activation Parameters

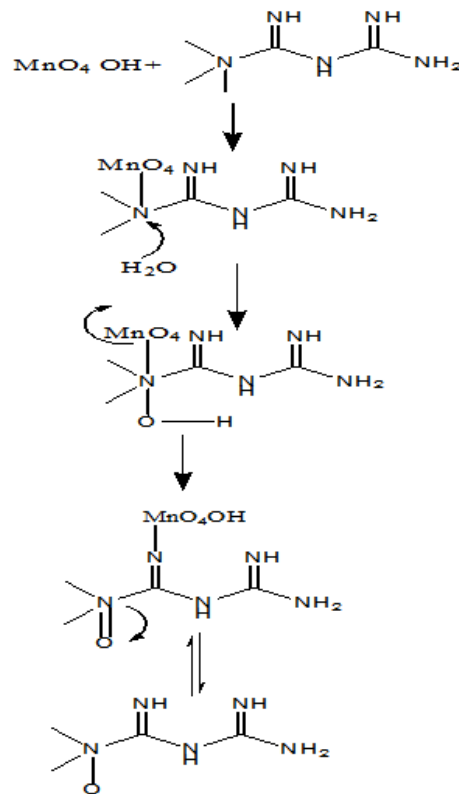
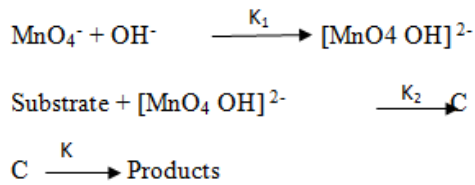
Parameters	Values
Ea	0.0012
$\Delta H^\ddagger$	-2477.57
$\Delta G^\ddagger$	86323.45
$\Delta S^\ddagger$	-297.99

#### Test for Free Radical (Study of Polymerization)

Polymerisation test: Acrylonitrile was added to the oxidized reaction mixture of the  $MnO_4$ . No gel formation was observed even on addition of excess of methanol. This suggests absence of free radical in the reaction mixture <sup>[11]</sup>.

Table 3: Effect of Varying Concentration of MET,  $KMnO_4$ , NaOH on the Rate of the Reaction at 298K

[MET] $\times 10^{-3}$ ( $mol\ dm^{-3}$ )	[ $KMnO_4$ ] $\times 10^{-4}$ ( $mol\ dm^{-3}$ )	[OH $^-$ ] $\times 10^{-1}$ ( $mol\ dm^{-3}$ )	KCl $\times 10^{-2}$ ( $mol\ dm^{-3}$ )	Kobs $\times 10^{-3}$ ( $mol\ dm^{-3}$ )	Kcal $\times 10^{-3}$ ( $mol\ dm^{-3}$ )
0.25	2.5	5	2.5	0.56	0.60
0.5	2.5	5	2.5	0.60	0.75
1	2.5	5	2.5	<b>0.89</b>	<b>0.95</b>
2	2.5	5	2.5	0.96	1.20
3	2.5	5	2.5	1.15	1.32
1	<b>0.5</b>	5	2.5	0.95	1.21
1	<b>1.5</b>	5	2.5	0.91	1.19
1	<b>2.5</b>	5	2.5	<b>0.89</b>	<b>0.95</b>
1	<b>5</b>	5	2.5	0.96	1.13
1	<b>7.5</b>	5	2.5	0.95	1.12
1	2.5	<b>1</b>	2.5	0.40	0.45
1	2.5	<b>3</b>	2.5	0.75	0.80
1	2.5	<b>5</b>	2.5	<b>0.89</b>	<b>0.95</b>
1	2.5	<b>7</b>	2.5	1.13	1.15
1	2.5	<b>10</b>	2.5	1.22	1.32
1	2.5	5	<b>1</b>	0.68	0.60
1	2.5	5	<b>2.5</b>	<b>0.80</b>	<b>0.95</b>
1	2.5	5	<b>5</b>	0.71	0.89

**SCHEME- I**

The permanganate in alkaline media combines with alkali to produce  $[\text{MnO}_4\text{OH}]^{2-}$  species in pre equilibrium step, as shown in scheme I. This supports with the fractional order of alkali the plot of  $1/k_{\text{obs}}$  v/s  $1/[\text{OH}^-]$  which is linear with non zero intercept. Many investigations suggest that many oxidation reactions proceed through intermediate complexes between oxidant and substrate. This is confirmed by the plot of  $1/K_{\text{obs}}$  versus  $1/[\text{sub}]$  which is in favour of possible formation of transient complex between oxidant and substrate comparable with Michaleis-menten mechanism. The reaction between substrates and alkali permanganate species confirmed by the insignificant effect of ionic strength in the reaction which is associated with reaction between ion and neutral molecule.

**SCHEME – II**

**From the Experimental Result, Scheme of Reaction is Given as Below**

$$\text{Rate} = \frac{-d[\text{MnO}_4^-]}{dt} = k[\text{complex-C}]$$

$$\text{Rate} = kK_2[\text{MET}][\text{MnO}_4\text{OH}]^{2-} \quad (1)$$

$$= k K_1 K_2 [\text{MET}]_f [\text{MnO}_4]_f [\text{OH}^-]_f$$

$$[\text{MET}]_T = [\text{MET}]_f \quad (2)$$

$$[\text{MnO}_4^-]_T = [\text{MnO}_4^-]_f + [\text{MnO}_4 \cdot \text{OH}]^{2-} + [\text{C}]$$

$$[\text{MnO}_4^-]_T = [\text{MnO}_4^-]_f + K_1 [\text{MnO}_4^-]_f [\text{OH}^-]_f + K_1 K_2 [\text{MET}] [\text{MnO}_4^-]_f [\text{OH}^-]_f$$

$$[\text{MnO}_4^-]_f = \frac{[\text{MnO}_4^-]_T}{1 + K_1 [\text{OH}^-]_f + K_1 K_2 [\text{MET}] [\text{OH}^-]_f} \quad (3)$$

$$[\text{MET}]_T = [\text{MET}]_f$$

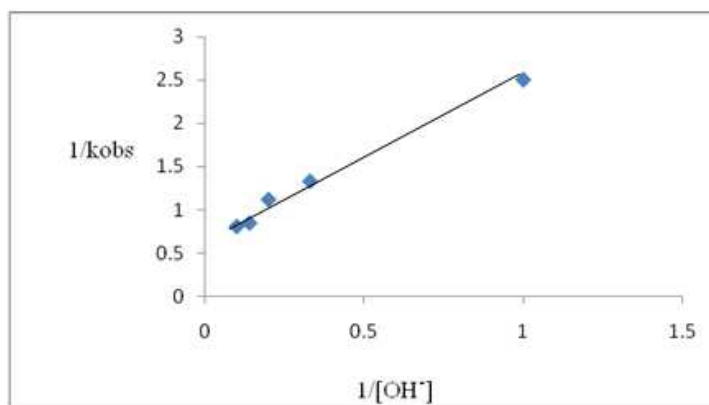
$$[\text{OH}^-]_T = [\text{OH}^-]_f$$

$$\text{Rate} = \frac{k K_1 K_2 [\text{MET}] [\text{MnO}_4^-] [\text{OH}^-]}{1 + K_1 [\text{OH}^-] + K_1 K_2 [\text{MET}] [\text{OH}^-]} \quad (4)$$

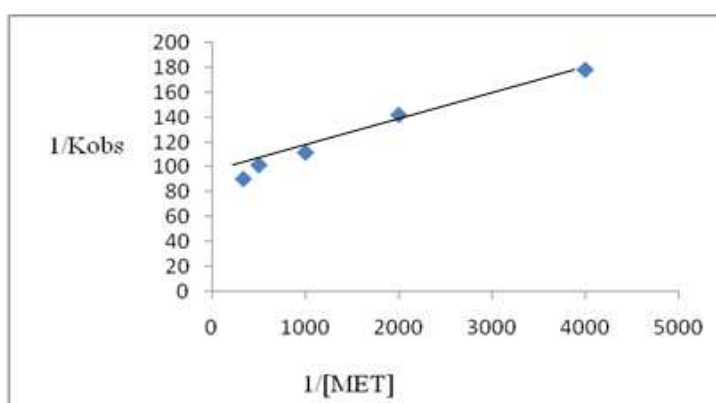
$$K_{\text{obs}} = \frac{\text{Rate}}{[\text{MnO}_4^-]} = \frac{k K_1 K_2 [\text{MET}] [\text{OH}^-]}{1 + K_1 [\text{OH}^-] + K_1 K_2 [\text{MET}] [\text{OH}^-]} \quad (5)$$

Rearranging 5, we get

$$\frac{1}{K_{\text{obs}}} = \frac{1}{k K_1 K_2 [\text{MET}] [\text{OH}^-]} + \frac{1}{k K_2 [\text{MET}]} + \frac{1}{k} \quad (6)$$



**Figure 7: Plot of 1/k<sub>obs</sub> v/s 1/[OH<sup>-</sup>] for the Verification of Rate Law.**



**Figure 8: Plot of 1/k<sub>obs</sub> v/s 1/[MET] for the Verification of Rate Law.**

By the slopes and the intercepts of above graphs, Fig (7) & (8), the values of  $k, K_1$  and  $K_2$  were calculated. By substituting  $k, K_1, K_2$  values in rate equation  $k$  experimental values were calculated. These are in good agreement with proposed mechanism.



## CONCLUSIONS

Oxidation of metformin HCl with potassium permanganate in aqueous basic medium was studied. Stoichiometry of oxidation MET was exhibiting 1:1. The product was found to be Metformin-N-Oxide. The reaction proceeds through the formation of complex between the substrate and species of permanganate. The temperature effect was studied and activation parameters were calculated. The large negative value of entropy ( $\Delta S^\ddagger$ ) suggest that the complex (C) is more ordered than the reactants<sup>[12]</sup>. Positive value of  $\Delta H^\ddagger$ ,  $\Delta G^\ddagger$  suggest the reaction is endothermic and non spontaneous.

## ACKNOWLEDGEMENT

We are thankful to the support and encouragement of Management and Principal of SEA College of Engineering and Technology, Bangalore India.

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