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RESEARCH ARTICLE

A Kinetic Study on the Oxidation of Pharmaceutically Significant PEG–400 by Periodate

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ABSTRACT:
Polyethylene glycol-400 (PEG-400) has a spectrum of applications in pharmaceutical field. PEG-400 oxidation was carried out in alkaline medium by using potassium periodate as an oxidant. Rate of the reaction was found to be first order dependence on the oxidant concentration. In the studied range, substrate concentration didn't change the reaction rate. Increase of alkali concentration decreased the reaction rate and order of the reaction with respect to alkali was inverse fractional. Effect of temperature on reaction rate was studied and then Arrhenius parameters were calculated. A suitable rate law was proposed based on the observed experimental results.

KEYWORDS: Polyethylene glycol-400, Oxidation, Alkaline medium, Potassium periodate, Kinetics

INTRODUCTION:
Polyethyleneglycol (PEG) is a well-known non-ionic polymer which is used in polymer-based drug delivery system[1]. In the drug delivery system, PEGs with different molecular weights (MW) are used[2]. PEGylation is a popular prodrug delivery system in which the interested molecule is covalently attached to PEG[3]. Protein molecules are associated with a good number of PEG molecules[4]. PEG is widely used in drug delivery and in preparation of bio-conjugates which are useful for diagnosis[5]. Due to cheap and environmentally safe nature, PEGs are popular solvent media to carryout reactions[6]. PEG-400 is recommended for momentary relief or protection against eye problems (like dryness irritation or burning)[7]. PEG 400 (Polyethylene glycol 400) belongs to low-molecular-weight grade of PEG series. A spectrum of pharmaceutical formulations use PEG-400, in view of its low toxicity. The other applications of PEG (200 to 8,000,000) include cosmetic field[8]. PEG-200 to PEG-600 are liquid PEGs and they are used as water miscible solubilizer in parenterals as well as oral liquids.

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PEG-400 is used in drugs delivery of injection dosage forms as per US FDA's Inactive Ingredient Guide (IIG)[9].

Exploration of reaction mechanism and deriving the laws which describe the reaction characteristics are possible by the study of reaction kinetics[10]. Out of the inorganic oxidants, well studied reactions used ceric[11], vanadate[12] and periodate[13,14]. 2,6-dichloro-quinone-4-chloro-imide[15,16], dichloro isocyanuric acid[17-20], chloromine-T[21] and N-bromo succinimide[22,23] were some of the well-used N-halo oxidants.

Many research papers discussed about oxidation of various types of substituted alcohols[21-23]. Fenton[24-26] and ceric (IV) ions[27,28] were the well-used oxidants in the oxidation of PEG. Inspite of non-disclosure of complete mechanism involved in the PEG oxidation by ceric ions, participation of free radicals was well established[27]. Mn/Ce composite oxide involved oxidation of PEG confirmed the participation of radical mechanism[29]. Formation of poly(oxyethylene)-dicarboxylic acids in high yields was reported in the oxidation by Jone's reagent at room temperature[30]. Rate law were proposed in the uncatalyzed and Ru (III) catalyzed permanganate oxidation of PEG[31]. Hence, in the present study, kinetic study of periodate oxidation of pharmaceutical importance of PEG-400 was carried out in aqueous alkaline medium.

EXPERIMENTAL:

In the current study, all the chemicals used were of analytical grade. Studied the reaction kinetics by iodometry. Periodate oxidation capacity was followed till its conversion to iodate, i.e., in the PEG-400 oxidation, two electrons transfer or one oxygen atom loss was observed per each periodate

RESULTS AND DISCUSSION:

Reaction orders of oxidant, substrate and alkali:

Order of reaction with respect to a particular reactant (oxidant/substrate/alkali) was measured by varying its concentration while concentration of each of other reactants was maintained at constant value. In the case of periodate, its concentration was changed from 0.00025 to 0.002 M. Plots of log (a-x) vs time (Fig. 1) resulted in linear curves (up to 85-90% of reactions) which shows that order of reaction w.r.t. [periodate] is unity. Rate constant values were found to be fairly constant in the studied range of [oxidant] (Table-1). It confirms the first order in [oxidant].

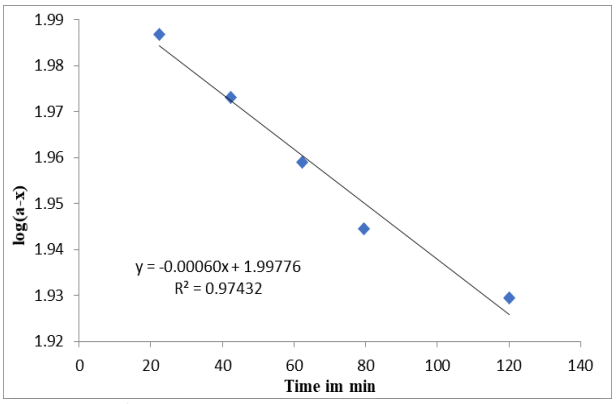

Fig. 1: Plot of log(a-x) versus time at [KIO_4] = 0.002 M, [PEG-400] = 0.025M, [OH^-] = 0.1 M and Temperature = 35 ºC

Table 1: Rate Constants in the Variation of Periodate Concentration

Reaction Conditions	Conc of Periodate (M)	$k_1 \times 10^4$ (min^{-1})
[PEG-400] = 0.025M [OH^-] = 0.1M Temperature = 35ºC	0.00025	15.25
	0.0005	14.90
	0.001	14.03
	0.002	13.80

Literature reports the substrate inhibition in sugar alcohols oxidation by KIO_4 in alkaline medium[13,14]. However, in the present case, rate constant is almost constant with the variation of [PEG-400] from 0.0025 to 0.1 M (Table-2). It indicates the zero order dependence of reaction on [substrate]. An increase of [OH^-] from 0.05 to 0.5 M had resulted in a decrease of reaction rate. The plot of log k_1 vs log [OH^-] shows the slope as –0.47 (Fig. 2) which indicates inverse fractional order w.r.t. [alkali].

Table 2. Reaction Rate Dependence on Concentrations of PEG-400 And Alkali

General Reaction Conditions	Variant	Conc of Variant (M)	$k_1 \times 10^4$ min^{-1}
[PEG-400] = 0.025 M [KIO_4] = 0.0005 M [OH^-] = 0.1 M Temperature = 35ºC	[Substrate]	0.0025	15.08
		0.0125	15.43
		0.025	14.90
		0.050	14.64
		0.10	14.45
	[Alkali]	0.05	18.55
		0.1	14.90
		0.2	10.58
		0.5	6.40

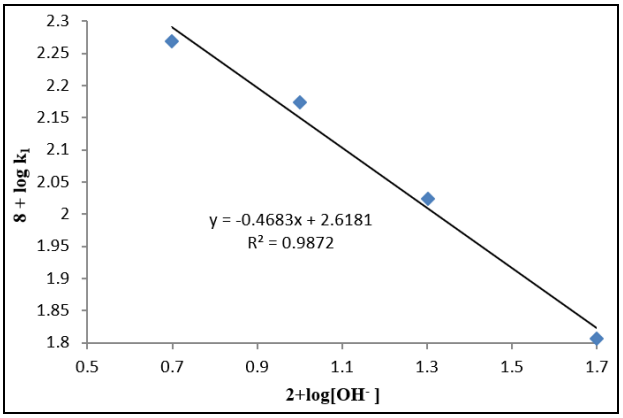

Fig. 2. Effect of alkali concentration on oxidation of PEG-400 by periodate

In alkaline medium, KIO_4 dissociates and equilibria (1–3) establish between the reactants and products[32]. The concerned equilibrium constants are shown below, which were measured by Aveston[32] at 298.2 K. The magnitude of periodate species distribution in aqueous alkaline solution can be calculated from the following equilibria. Out of the four periodate species, $[H_2IO_6^{3-}]$ and $[H_3IO_6^{2-}]$ are considerable as $[IO_4^-]$ and $[H_2I_2O_{10}^{4-}]$ are insignificant in the range of used alkali concentrations. Crouthamel's data[33] was used to calculate their concentrations which are found to be in lines with other researcher's findings[34-36].

$$2IO_4^- + 2OH^- \rightleftharpoons H_2I_2O_{10}^{4} \qquad \log K_1 = 15.05 \rightarrow \quad (1)$$

$$IO_4^- + OH^- + H_2O \rightleftharpoons H_3IO_6^{2-} \qquad \log K_2 = 6.21 \rightarrow \quad (2)$$

$$IO_4^- + 2OH^- \rightleftharpoons H_2IO_6^{3-} \qquad \log K_3 = 8.67 \rightarrow \quad (3)$$

As per Shan[37], the given below equations (4) and (5) can be obtained from the above equilibria (2) and (3)

$$H_2IO_6^{3-} = \frac{\beta_3[OH^-]^2}{1+\beta_2[OH^-]+\beta_3[OH^-]^2}[IO_4^-]_{ex} = f([OH^-])[IO_4^-]_{ex} \rightarrow \quad (4)$$

$$H_3IO_6^{2-} = \frac{\beta_2[OH^-]}{1+\beta_2[OH^-]+\beta_3[OH^-]^2}[IO_4^-]_{ex} = \emptyset([OH^-])[IO_4^-]_{ex} \rightarrow \quad (5)$$

Where, $[IO_4^-]_{ex}$ represents the actual total concentration

of periodate. Since $[H_3IO_6^{2-}]$ and $[H_2IO_6^{3-}]$ are the two chief species of periodate, sum of their concentrations is nearly corresponding to $[IO_4^-]_{ex}$. Therefore, these two species complex with PEG-400. Concentrations of these two species were calculated using the above equations at various alkali concentrations in the range of 0.025 to 0.5 M. Concentrations of $[H_3IO_6^{2-}]$ and $[H_2IO_6^{3-}]$ at different concentrations (0.025, 0.05, 0.10, 0.20 and 0.50) are (0.000107, 0.000180, 0.000267, 0.000349 and 0.000427) and (0.000364, 0.000308, 0.000228, 0.000149 and 0.000073) respectively. It indicates that $[H_2IO_6^{3-}]$ is the predominant species at higher concentration of alkali but it was $[H_3IO_6^{2-}]$ at lower alkali concentration.

Temperature dependence:

Increase of temperature from 35 to 50 °C raised k_1 (first order rate constants). A plot of log (k_1) *vs.* 1/T (Fig.3) resulted in a straight line. Calculated the activation parameters from Eyring equation and slope of the plot[38]. Values are listed out in the Table – 3.

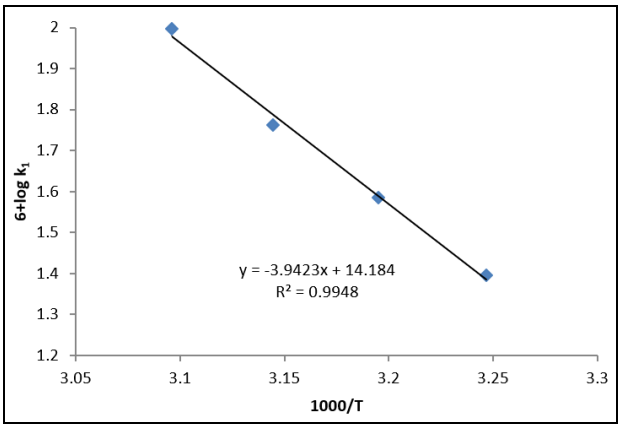

Fig. 3: Effect of temperature on oxidation of PEG-400 by periodate

Table 3: Arrhenius Parameters at 308 K

Activation energy ($\Delta E^{\neq}$ KJ/mole)	Enthalpy of activation ($\Delta H^{\neq}$ KJ/mole)	Entropy of activation ($-\Delta S^{\neq}$ J/K/mole)	$\log_{10} P_Z$	Gibb's free energy ($\Delta G^{\neq}$ KJ/mole)
75.48	72.92	96.65	8.19	102.69

Effect of boric acid and salts:

As per the earlier reports, the rate of reaction was increased by the boric acid addition in alkaline medium. Because, borate ions form complexes with sugar alcohols (inositol/sorbitol/mannitol) in view of favored condtions[13,14]. In those cases, substrate inhibition was described in terms of a competition in the formation the above complex with that of a stable complex between periodate and sugar alcohol(s). However, reaction rate was not affected by the addition of boric acid in the present case (Table-4). PEG-400 has a hydroxyl value[39] of 264 to 300. So, out of the good number of hydroxyl groups present on each PEG-400, some of the hydroxyl groups on it involve in the formation of complex with the highly dissociating potassium borate. Hence, the balance hydroxyl groups on substrate will be free. A decrease in the reaction rate was observed by the adding salts of halides (chloride and iodide ions). But the reaction rate was doubled by the addition of bromide ions.

Table 4: Effect of Salt and Boric Acid Concentrations on Reaction Rate

General Reaction Conditions	Variant	Nature of Variant / Variant Conc (M)	$k_1 \times 10^4$ min^{-1}
[PEG-400] = 0.025 M [KIO_4] = 0.0005 M [Salt] = 0.1M [OH^-] = 0.1M Temperature = 35°C	Salt	Nil	14.90
		KCl	14.47
		KBr	30.22
		KI	3.04
		KNO_3	19.47
	[Boric Acid]	0	14.90
		0.01	14.13
		0.025	13.46
		0.05	14.90

Nature of reaction and rate law:

Spot tests were used to recognize the reaction end products[40]. The major reaction products were long chain aldehydes. In addition, because of complete oxidation, a slight amount of carboxylic acids were also observed. Further conversion to 2,4-dinitrophenyldrazone derivatives established the formation of aldehydes. The stated products nature in the present study is substantiated from the earlier reports of Szymański et al[27]. End –OH groups present on PEGs display considerable effect on their properties (both physical and chemical properties). Therefore, 'polyethylene glycols' is the prevailing name for these molecules where, 'polyethylene oxides' is their technical name[41]. Besides to the active nature of hydroxyl groups, their hydroxyl values are high. Consequently, oxidation of end –OH groups takes place to yield the above mentioned products. But, definite stoichiometry was not observed. A rate law is offered taking into consideration of the above mentioned orders of the reactants. In addition to the available simple methods for the pharmaceutical formulations[42-43], the usage of biocompatible polymers is the thrust research area in the pharmaceutical field[44-53]. Hence, a rate law is proposed as shown below for the oxidation of the pharmaceutically significant PEG-400 in alkaline medium.

The two main periodate species ($H_3IO_6^{2-}$ and $H_2IO_6^{3-}$) form complexes (C_1 and C_2) with PEG and equilibria exist between them. At a slower rate, these two complexes decompose to yield products with rate constants of k_1 and k_2 respectively.

$$H_3IO_6^{2-} + \text{PEG-400} \underset{}{\overset{K_4}{\rightleftharpoons}} \text{Complex } C_1 \xrightarrow{k_1} \text{Products}$$

$$H_2IO_6^{3-} + \text{PEG-400} \overset{K_5}{\rightleftharpoons} \text{Complex } C_2 \xrightarrow{k_2} \text{Products}$$

$[IO_4^-]_T$, total concentration of periodate can be written as

$[IO_4^-]_T = [IO_4^-] + [H_2I_2O_{10}^{4-}] + [H_3IO_6^{2-}] + [H_2IO_6^{3-}] +$ [Complex C_1] + [Complex C_2]

In view of insignificant concentrations of $[IO_4^-]$ and $[H_2I_2O_{10}^{4-}]$, the above equation turns to

$[IO_4^-]_T = [H_3IO_6^{2-}] + [H_2IO_6^{3-}] +$ [Complex C_1] + [Complex C_2]

It is known that hydroxyl value of PEG-400 ranges[39] from 264 to 300 and hence, good number of hydroxyl groups is available on every PEG-400 molecule. In addition, the concentration of PEG-400 is almost fifty times higher than periodate concentration. It leads to complexation of almost all $H_3IO_6^{2-}$ and $H_2IO_6^{3-}$ species with –OH groups present on PEG-400. Henceforth, free oxidant species will not be further available. Therefore, in the above equation, the first two terms can be ignored. It leads to the following equation.

$[IO_4^-]_T$ = [Complex C_1] + [Complex C_2]

$= K_2K_4$ [PEG-400] $[IO_4^-]$ $[OH^-] + K_3K_5$ [PEG-400] $[IO_4^-]$ $[OH^-]^2$

$$[IO_4^-] = \frac{[IO_4^-]_T}{[OH^-][PEG-400]\{K_2K_4 + K_3K_5[OH^-]}$$

$$\text{Rate} = k_1[\text{Complex } C_1] + k_2[\text{Complex } C_2]$$

$= k_1K_4$ $[H_3IO_6^{2-}]$ [PEG-400] + k_2K_5 $[H_2IO_6^{3-}]$ [PEG-400]

where $[H_3IO_6^{2-}] = K_2$ $[IO_4^-]$ $[OH^-]$ and $[H_2IO_6^{3-}] = K_3$ $[IO_4^-]$ $[OH^-]^2$

Rate = $[IO_4^-]$ $[OH^-]$ [PEG-400] $\{k_1K_2K_4 + k_2K_3K_5$ $[OH^-]\}$

$$\text{Rate} = \frac{[IO_4^-]_T[OH^-][PEG-400]\{k_1K_2K_4 + k_2K_3K_5[OH^-]\}}{[OH^-][PEG-400]\{K_2K_4 + K_3K_5[OH^-]}$$

$$= \frac{[IO_4^-]_T[PEG-400]\{k_1K_2K_4 + k_2K_3K_5[OH^-]\}}{[PEG-400]\{K_2K_4 + K_3K_5[OH^-]\}}$$

$$= \frac{[IO_4^-]_T\{k_1K_2K_4 + k_2K_3K_5[OH^-]\}}{\{K_2K_4 + K_3K_5[OH^-]\}}$$

First order reaction in [oxidant] and independence of reaction w.r.t. [PEG-400] are explained by the above rate law. Since $k_2 << 1$, hydroxide ion value is lower in the numerator in comparison to that of denominator. It helps to explain the inverse fractional order in alkali concentration.

CONCLUSION:

In order to learn the stability of pharmaceutically significant PEG-400 in presence of oxidants and nature of products formed, its oxidation was carried out in alkaline medium. Two electrons transfer or one oxygen atom loss was observed per each periodate in the PEG-400 oxidation. The reactions were independent of PEG-400 concentration. Inverse fractional order dependence of reaction was observed with alkali concentration. In consistent with the observed results, a suitable rate law was postulated.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

LIST OF SYMBOLS AND ABBREVIATIONS:

PEG : Polyethylene Glycol,
NBS : N-Bromosuccinimide,
DCICA : Dichloroisocyanuric Acid,
DCQCI : 2, 6-Dichloroquinone-4-Chloro-Imide
CAT : chloramine-T
k_1 : First order rate constant.
$\Delta E^{\neq}$: Activation energy
$\mathbf{\Delta H^{\neq}}$: Enthalpy of activation
$\mathbf{\Delta G^{\neq}}$: Gibb's free energy
$\Delta S^{\neq}$: Entropy of activation

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