

PERIODATE OXIDATION OF PEG-600, AN ESSENTIAL PHARMACEUTICAL POLYMER

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ABSTRACT

Objective: To study the kinetics of periodate oxidation of polyethylene glycol-600 (PEG-600), a familiar non-toxic polymer used in pharmaceutical and other fields of industry.

Methods: Reactions were carried out in alkaline medium and measured the kinetics by iodometry. One oxygen atom loss or two electrons transfer was observed per each molecule of periodate i.e., the rate of reaction was measured periodate converts to iodate because the formed iodate species is unable to oxidize the substrate molecules.

Results: Based on log (a-x) versus t plots, order w. r. t. oxidant (periodate) is unity. Reactions were found to be independent of substrate (PEG-600) concentration. A decrease in rate with an increase in alkali concentration [OH⁻] was found and order was inverse fractional. Temperature dependence of reaction rate was studied and then calculated the corresponding Arrhenius parameters.

Conclusion: An appropriate rate law was proposed by considering the above experimental results.

Keywords: PEG-600, Alkaline medium, Periodate, Oxidation, Kinetics

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INTRODUCTION

Liquid polyethylene glycols (PEG 200-600) are used in parenteral as well as oral liquids. Polyethylene glycols (PEGs) are utilized in various pharmaceutical preparations which are useful for different routes of administration including oral (capsule, tablet and solution) and intravenous (injection) [1]. In drug delivery systems, PEGs play a vital role [2]. PEGs (200 to 8,000,000) are widely applicable in cosmetics [3]. Toxic substances from the surface of burned skin can be removed by using liquid PEGs as antidotes [4]. PEGs exhibit good phase transfer features and excellent solvent properties which can be integrated into an effective integrated system (known as ABRE-aqueous biphasic reactive extraction) which enables separation of catalysts and/or reactants from products [5]. Mechanical properties of concrete are improved by the usage of polyethylene glycol as self-curing agent [6, 7].

Among other PEGs, PEG-600 is widely used to understand the intestinal physiology in human beings as it has low toxicity and freely excreted along with urine [8]. It is also extensively useful in the preparation of ointment bases and as a food additive. PEG-600 is also used for the preparation of membranes from Cellulose Acetate [9]. PEG 600 acts as an excellent environment-friendly surfactant in combination with polysorbate 20 in inhibition of zinc composite corrosion in presence of alkaline medium [10]. PEG 600 is used during dyeability of fabric. The process improves fabric sustainability as PEG acts as a swelling agent [11].

Study of reaction rate constants is useful for investigation of reaction mechanism and to derivation of rate laws to explain the observations [12]. Literature collection shows that kinetics of oxidation reactions involving N-halo oxidants [13-21] and inorganic oxidants [22, 23] were well studied. Similarly, researchers are interested in the study of oxidation of various substituted alcohols [13, 14, 21] including polyethylene glycols and especially, ceric (IV) ions [24, 25] and Fenton [26-28] were the best used oxidants. Catalytic amounts of Mn/Ce composite oxide direct the oxidation of PEG to a radical mechanism [29]. Similarly, the involvement of free radicals was proposed using Ce(IV) oxidant in sulphuric acid

medium in spite of the incomplete understanding of mechanism [24]. Poly(oxyethylene)-dicarboxylic acids were resulted in high concentrations in the room temperature oxidation of PEGs by Jone's reagent [30, 31] proposed two different stages in the uncatalyzed oxidation of PEG by permanganate and also studied the Ruthenium (III) influence. As periodate oxidation of PEG-600 was not studied earlier, it was considered for the present study taking into consideration of its wide industrial and pharmaceutical usage.

MATERIALS AND METHODS

In the current study, all the chemicals used were analytical grade purity. Reaction kinetics were measured by iodometry [32, 33]. In the PEG-600 oxidation, one oxygen atom loss or two electrons transfer was observed per each molecule of potassium periodate (KIO₄) i.e., the rate of reaction was measured periodate converts to iodate because, the formed iodate species is unable to oxidize the substrate molecules. Further confirmed the same by conducting the experiments separately with iodate [12, 32, 33].

RESULTS AND DISCUSSION

Reaction orders of oxidant

To understand the order of reaction w. r. t. [oxidant], periodate concentration was altered from 0.00025 to 0.002 M, whereas maintained the concentrations of other reactant at constant values (table 1). Graphs were drawn between log (a-x) vs time (fig. 1). Linear curves were observed up to about 2/3rd of the reaction. It indicates first order reactions w. r. t. [periodate]. In addition, confirmed the first order kinetics from almost constant reaction rate values in the range of studied oxidant concentration.

Reaction orders of substrate and alkali

Independence of reaction rate on [substrate] was observed because, reaction rates were almost constant by changing the concentration of PEG-600 in the range of 0.0025 to 0.1 M. In contrast, literature survey shows that a decrease in reaction rate with an increase in substrate concentration was noted in the oxidation of sugar alcohols by KIO₄ in alkaline medium [32, 33].

Table 1: Variation of [periodate] and rate constants

Conc of periodate (M)	$k_1 \times 10^4 \text{ (min}^{-1}\text{)}$
0.00025	5.62
0.0005	5.30
0.001	5.16
0.002	5.07

Reaction conditions:
 [PEG-600] = 0.025 M
 Temperature = 35 °C [OH⁻] = 0.1 M

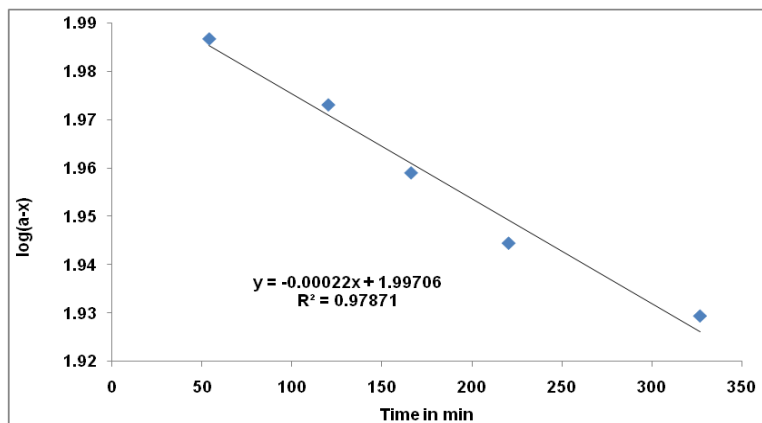


Fig. 1: Plot of log(a-x) versus time at [KIO₄] = 0.002 M, [PEG-600] = 0.025 M, [OH⁻] = 0.1 M and Temperature = 35 °C

Table 2: Reaction rate variation with [PEG-600] and [alkali]

Variant	Conc of variant (M)	$k_1 \times 10^4 \text{ min}^{-1}$
[Substrate]	0.0025	5.43
	0.0125	5.35
	0.025	5.30
	0.05	5.26
	0.1	5.69
[Alkali]	0.05	7.13
	0.1	5.30
	0.2	4.51
	0.5	3.34

General reaction conditions:
 [PEG-600] = 0.025 M [KIO₄] = 0.005 M
 Temperature = 35 °C [OH⁻] = 0.1 M

Concentration of alkali was increased in the range of 0.05 to 0.5 M, where, reaction rate was decreased. A graph of log k₁ vs log [OH⁻]

shows a linear curve with a slope of -0.32 (fig. 2). It indicates the inverse fractional order of reaction in [alkali].

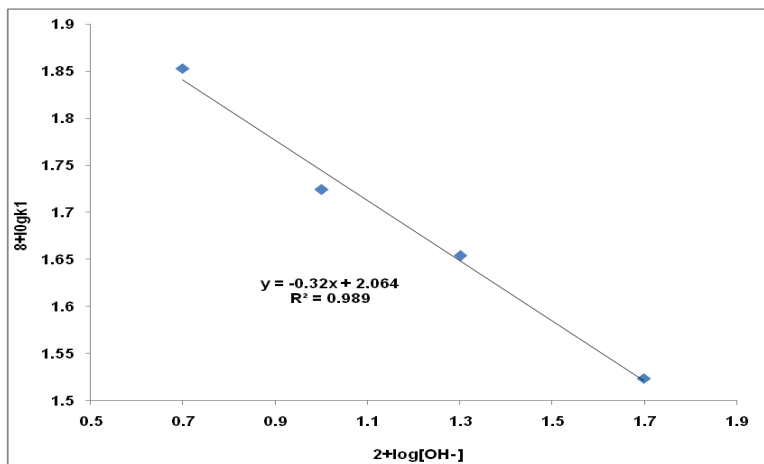
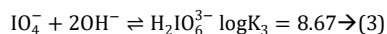
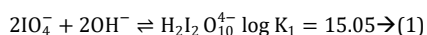


Fig. 2: Effect of alkali concentration on oxidation of PEG-600 by periodate

Dissociation of potassium periodate takes place in alkaline medium [34] and results in establishment of equilibrium conditions between the products with those of reactants (1-3). The following equations show values of K₁, K₂ and K₃ (relevant equilibrium constants) which were shown at 298.2 K.



The degree of existence of periodate species in aqueous alkaline medium can be calculated with the help of above equilibria. Out of the four species of periodate, concentrations of species-1 and 2 O_4^- and $\text{H}_2\text{I}_2\text{O}_{10}^{4-}$ are insignificant at the level of maintained hydroxide ion concentration. Hence, the available species at high concentrations are species-3 and 4 ($\text{H}_2\text{IO}_6^{3-}$ and $\text{H}_3\text{IO}_6^{2-}$), the concentrations of which can be determined with the support of

Crouthamel's data [35] (1951) in similar passion to others [36-38]. Hence, the sum of concentration of these two active species ($\text{H}_3\text{IO}_6^{2-}$ and $\text{H}_2\text{IO}_6^{3-}$) can be considered as equivalent to the overall periodate ion concentration which is denoted by $[\text{IO}_4^-]_{\text{ex}}$. The given below equations (4) and (5) were proposed by J. H. Shan [39] based on the above equilibria (2) and (3).

$$\text{H}_2\text{IO}_6^{3-} = \frac{\beta_3[\text{OH}^-]^2}{1+\beta_2[\text{OH}^-]+\beta_3[\text{OH}^-]^2} [\text{IO}_4^-]_{\text{ex}} = f([\text{OH}^-])[\text{IO}_4^-]_{\text{ex}} \rightarrow (4)$$

$$\text{H}_3\text{IO}_6^{2-} = \frac{\beta_2[\text{OH}^-]}{1+\beta_2[\text{OH}^-]+\beta_3[\text{OH}^-]^2} [\text{IO}_4^-]_{\text{ex}} = \phi([\text{OH}^-])[\text{IO}_4^-]_{\text{ex}} \rightarrow (5)$$

Variation of concentrations of periodate species with concentration of alkali (fig. 3). A gradual increase in $\text{H}_2\text{IO}_6^{3-}$ concentration was observed with an increase in alkali concentration while a reverse phenomenon i.e., a gradual decrease in $\text{H}_3\text{IO}_6^{2-}$ concentration was noticed. So, these two species can complex with PEG-600.

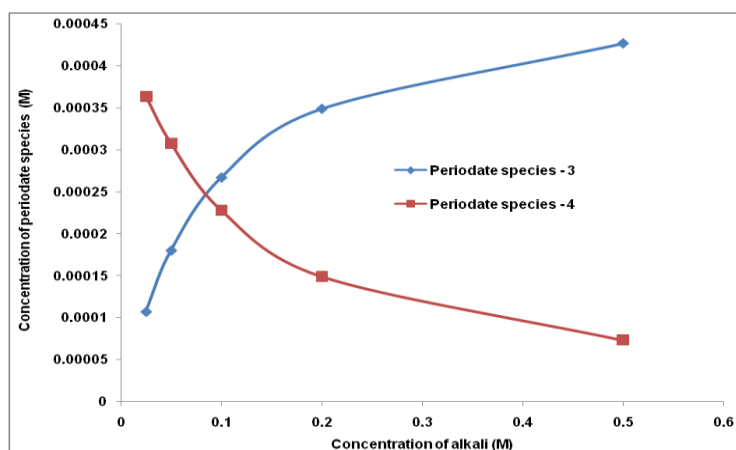


Fig. 3: Variation of concentrations of periodate species with different concentrations of alkali

Temperature effect

First-order rate constants (k_1) were measured at different concentrations from 35 to 50 °C, where an increase in rate constant was observed with an increase in temperature. $\log(k_1)$ was plotted

against $1/T$ to give a straight line (fig. 4). Thermodynamic parameters were determined using Eyring equation and slope of the plot [40]. Tabulated the values of activation parameters (ΔE^\ddagger , ΔH^\ddagger , ΔG^\ddagger and $-\Delta S^\ddagger$) (table 3).

Table 3: Arrhenius parameters at 308 K

ΔE^\ddagger KJ/mole	ΔH^\ddagger KJ/mole	$-\Delta S^\ddagger$ JK ⁻¹ /mole	$\log_{10} P_z$	ΔG^\ddagger KJ/mole.
79.25	76.69	93.00	8.38	105.33

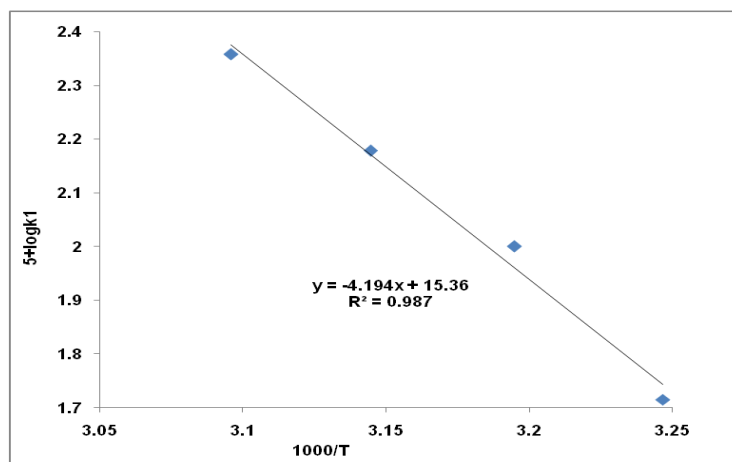


Fig. 4: Dependence of reaction rate on temperature variation

Boric acid and salts effect

Literature survey indicates an improvement of reaction rate in alkali medium by the addition of boric acid in the periodate oxidation of different sugar alcohols [32, 33]. It was due to the favoured conditions to complex the sugar alcohols with borate ion. So, it gives a competition to form a stable complex of periodate with sugar alcohols. Hence, explained the observed substrate inhibition in such cases. However, in this

study, no much alteration in reaction rate was observed after boric acid addition (table 4). It might be due to good number of hydroxyl groups in view of reasonable hydroxyl value of [41] PEG-600 in the range of 178–197. So, inspite of complexing of greatly ionisable potassium borate with certain -OH groups on PEG-600, the balance free hydroxyl groups number on substrate is also substantially high. Doubling of reaction rate was observed with the addition of bromide ions while, rate was retarded by the inclusion of chloride or iodide ions.

Table 4: Reaction rate variation with [salt] and [boric acid]

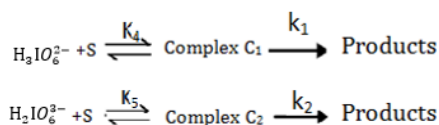
Variant	Nature of Variant/Variant Conc (M)	$k_1 \times 10^4 \text{ min}^{-1}$
Salt	0	5.30
	KCl	3.72
	KBr	13.27
	KI	1.78
	KNO ₃	5.29
[Boric Acid]	0	5.30
	0.01	4.91
	0.025	5.33
	0.05	5.51

General Reaction Conditions:
 [PEG-600] = 0.025 M [KIO₄] = 0.005 M
 Temperature = 35 °C [OH⁻] = 0.1 M
 [Salt] = 0.1 M

Rate law of equation

The principal reaction products in the present study were long chain aldehydes along with a negligible extent of carboxylic acids in view of thorough oxidation. The nature of final products was identified using spot tests [42]. Conversion to 2,4-dinitrophenyldrazones further established the formation of aldehydes. Nature of products are in the same order that reported by Szymański JK *et al.* [24]. Though the technical name of these substrates is 'polyethylene oxides', but commonly called as polyethylene glycols because the terminal -OH groups present on these display an ample effect on physical properties and also on chemical properties [43]. Besides to it, hydroxyl value is also reasonably high. Hence, the oxidation of terminal hydroxyl groups resulted in the products noticed. Difficulty was faced while recording the precise stoichiometry. Suggested a rate law taking into consideration of the above kinetic orders.

As discussed above, available species in reasonable quantities are H₂IO₆³⁻ and H₃IO₆²⁻. They form complexes C₁ and C₂ respectively with the substrate (PEG-600), which dissociate at slower rate to form products.



We know that $[\text{IO}_4^-]_{\text{T}} = [\text{IO}_4^-] + [\text{H}_2\text{IO}_6^{3-}] + [\text{H}_3\text{IO}_6^{2-}] + [\text{H}_2\text{IO}_6^{3-}] + [\text{Complex C}_1] + [\text{Complex C}_2]$

Where $[\text{IO}_4^-]_{\text{T}}$ represents the total concentration of periodate and it can be rewritten as given below by taking into consideration of $[\text{IO}_4^-]$ and $[\text{H}_2\text{IO}_6^{3-}]$ as negligible.

$$[\text{IO}_4^-]_{\text{T}} = [\text{H}_3\text{IO}_6^{2-}] + [\text{H}_2\text{IO}_6^{3-}] + [\text{Complex C}_1] + [\text{Complex C}_2]$$

$$= K_2 [\text{IO}_4^-][\text{OH}^-] + K_3 [\text{IO}_4^-][\text{OH}^-]^2$$

$$+ K_2 K_4 [\text{S}][\text{IO}_4^-][\text{OH}^-] + K_3 K_5 [\text{S}][\text{IO}_4^-][\text{OH}^-]^2$$

We can presume the non-availability of any uncomplexed periodate ions (H₃IO₆²⁻ and H₂IO₆³⁻) because they are totally complexed with -OH groups present on substrate molecules in view of large number of hydroxyl groups in the range [41] of 178–197. Hence, the above

equation can be rewritten as given below by omitting the negligible quantities (H₃IO₆²⁻ and H₂IO₆³⁻).

$$[\text{IO}_4^-]_{\text{T}} = K_2 K_4 [\text{S}][\text{IO}_4^-][\text{OH}^-] + K_3 K_5 [\text{S}][\text{IO}_4^-][\text{OH}^-]^2$$

$$\begin{aligned} \text{Rate} &= k_1 [\text{Complex C}_1] + k_2 [\text{Complex C}_2] \\ &= k_1 K_4 [\text{H}_3\text{IO}_6^{2-}][\text{S}] + k_2 K_5 [\text{H}_2\text{IO}_6^{3-}][\text{S}] \\ &= k_1 K_2 K_4 [\text{IO}_4^-][\text{OH}^-][\text{S}] + k_2 K_3 K_5 [\text{IO}_4^-][\text{OH}^-]^2 [\text{S}] \\ &= [\text{IO}_4^-][\text{OH}^-][\text{S}] \{k_1 K_2 K_4 + k_2 K_3 K_5 [\text{OH}^-]\} \\ &= \frac{[\text{IO}_4^-]_{\text{T}} [\text{S}] \{k_1 K_2 K_4 + k_2 K_3 K_5 [\text{OH}^-]\}}{[\text{S}] \{K_2 K_4 + K_3 K_5 [\text{OH}^-]\}} \\ &= \frac{[\text{IO}_4^-]_{\text{T}} \{k_1 K_2 K_4 + k_2 K_3 K_5 [\text{OH}^-]\}}{\{K_2 K_4 + K_3 K_5 [\text{OH}^-]\}} \end{aligned}$$

First order reaction in [oxidant] and zero order in [S] are explained by the above rate law. Value of k₂ is very less than unity and hence, hydroxide concentration is very small than that of value in denominator. Henceforth, inverse fractional order in [OH⁻] is explained.

In view of the present focus of research on applications of natural polymers in pharmaceutical and other fields [44-46], the outcome of the present study help to understand the stability of familiar non-toxic polymer (PEG-600) in presence of periodate in alkaline medium.

CONCLUSION

An appropriate rate law was proposed for the periodate oxidation of PEG-600, a pharmaceutical polymer in alkaline medium. Long chain aldehydes were the prime final product with insignificant degree of carboxylic acids. The present study helps to understand the stability of the polymer.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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