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Kinetics of periodate oxidation of polyoxyethylene – 300, a biodegradable pharmaceutical polymer

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ABSTRACT

Polyoxyethylene – 300 (POE) is a well-known biodegradable pharmaceutical polymer. In order to understand the stability of POE and to derive the reaction rate law, the title reaction was carried out in aqueous alkaline medium. Reaction was found to be first order dependent on the concentration oxidant (periodate) and independent of substrate (POE) concentration. A retardation of reaction rate with an increase in hydroxide concentration shows an inverse fractional order in it. Based on the studies of the temperature dependence of reaction, evaluated the activation parameters.

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INTRODUCTION

Poly oxyethylene (POE) is a freely obtainable polymer in an array of molecular weights. A variety of POEs exhibit solubility in water and some of the organic solvents. The other name is PEG (poly ethylene glycol) when its molecular weight is less than one lakh. PEGs (having a molecular weight less than a thousand) are colorless and viscous liquids (Bailey and Koleske, 1976). Polyethylene glycols (PEGs) are well-known excipients (Debotton and Dahan, 2017). In controlled drug delivery, PEG copolymers with polylactic acid (PLA) are used (Xu *et al.*, 2019). Protein-based medications accumulate the protein deposits in the blood, which can be reduced by opting PEG surface coating on them (Van Antwerp *et al.*, 2002). Osmotic action of PEG supports its usage as a laxative (Savino *et al.*, 2012). Liquid PEGs (200 - 600) are used in pharmaceutical preparations of oral and intravenous administration (D'souza and Shegokar, 2016). As antidotes, they remove the toxic substances from the surface of burned skin (Cartotto *et al.*, 1996).

In addition, a spectrum of industrial applications is shown by PEGs. In view of low toxicity, cheap cost, biodegradability and ready availability, PEGs possess high advantage for solvents (Zhang *et al.*, 2004). In addition, PEG is a well-known phase transfer catalyst (Xie *et al.*, 2000) and reducing agent in organic synthesis in the presence of microwave irradiation (Bendale and Khadilkar, 2000; Sauvagnat *et al.*, 2000). Chromeno[3,4-*b*] quinoline derivatives were synthesized efficiently in a "green" solvent like PEG 300 using Cu(II)BHPPDAH complex as heterogeneous catalyst (Sharghi *et al.*, 2013). In most of the cross-coupling reactions, PEGs are used as effective green solvents (Razler *et al.*, 2009). PEG-300 was proved to be an excellent medium to result in high yields of the biaryl nucleus in a cross-coupling of aryl chlorides and phenylboronic acids through Suzuki–

Miyaura cross-coupling (Yin *et al.*, 2006). Under thermal conditions, high yields (98%) of 1-iodo-4-nitrobenzene and phenylboronic acid were obtained by carrying out Suzuki cross-coupling reactions in PEG-300 (Silva, 2010). Dziurka (2005) included PEG 300 in resin mixture and studied its influence on the properties of PMDI resin. PEG is also used as a solvent in the preparation of inorganic nano-materials like TiO_2 nanoparticles in a sol-gel method (Liu *et al.*, 2000) and silver nanorods by an electrochemical technique (Zhu *et al.*, 2001) Bhattacharjee *et al.* (2002) proposed a method to synthesize CdS nanoparticles implanted in a matrix made up of PEG 300. Variation of PEG-300 concentration played a critical role in the size and orientation of formed PbS nanoparticles. Increase in [PEG] decreased the reaction rate. It leads to a decrease in film thickness and hence an increase in transmittance of film. At the same time, optical band gaps increase with an increase in [PEG] (Kaci *et al.*, 2010). 1D nanostructural materials are prepared by using structure-directing agents like PEG polymers (Shi *et al.*, 2007). Hexagonal ZnO micro nuts (HZMNs) were prepared in a hydrothermal method by using Zn(II)-PEG 300 globules as a soft template (Shi *et al.*, 2009). PEG-300 was used as a surfactant in a hydrothermal route for the preparation of rectangle rod-like shaped $4ZnO.B_2O_3.H_2O$, which can be used as a flame-retardant filling material (Shi *et al.*, 2007). Similarly, the two-phase system consisting of PEG along with aqueous KCl, was used to extract the metal ions (like Zn^{+2} and Cu^{+2}) (Ammar *et al.*, 2011).

Ulbricht *et al.* (2014) reported the oxidative degradation of PEGs in appropriate conditions. (Per) Oxidation of PEGs is very well known (Han *et al.*, 1997). PEG 200 and 300 are degraded by *Alcaligenes faecalis* var. *denitrificans* during their anaerobic growth (Grant and Payne, 1983). Literature survey shows the oxidation of PEGs by different oxidants like ceric (IV) ions Szymansi *et al.* (2015) (Nagarajan *et al.*, 1994), Mn/Ce composite oxide (Imamura *et al.*, 1986), permanganate (Hassan *et al.*, 2018), Jone's reagent (Lele and Kulkarni, 1998) and Fenton reagent (Chen *et al.*, 2014; Prousek and Duriskova, 1998). Since the oxidation of PEG-300 by periodate was not studied so far, it is considered for the current study.

MATERIALS AND METHODS

Different concentrations of oxidant (potassium periodate), the substrate (POE) were thermostatted at a constant temperature (35±0.1 °C) for two hours. In all the cases, substrate concentration was kept higher compared to oxidant. Determined the unreacted oxidant concentration by iodometry. Reproducibility of reaction rate constants was found to be with in ± 5%. Transfer of two electrons or loss of one atom of oxygen per oxidant molecule was measured, i.e., conversion of periodate up to iodate, as the latter is incapable of oxidizing the PEG-300 (POE) molecules. Iodate was used to conduct separate experiments to endorse the above reactions. Alkalinity was maintained by using sodium hydroxide. Taking into consideration of the maintained fair alkali concentrations in the present condition, its effect was studied. Reaction vessels surface has no effect on the reaction rate, and it was confirmed from the obtained identical results with acrylic and quartz ware. Dissolved oxygen has no influence on reaction as the difference is insignificant in the rate constants obtained in the presence of air and under nitrogen atmosphere.

RESULTS AND DISCUSSION

Reaction orders

Adopted the uni-variant method to determine the reaction orders w.r.t. concentrations of periodate / POE / alkali, in which rate constants were measured by changing the concentration of one variant while maintaining constant experimental conditions as well as concentrations of balance reagents involved (Table 1). Varied the periodate concentration over the range of 0.00025 to 0.002 M at fixed conditions of [POE], [OH^-] and temperature (Table 1). Insignificant effect of periodate concentration on the reaction rate was noticed, i.e., pseudo-first-order rate constants (k_1) were almost constant with the variation of periodate concentration in the above range. First-order nature of reaction was also evident from the linearity of plots obtained in log [periodate] versus time (Figure 1).

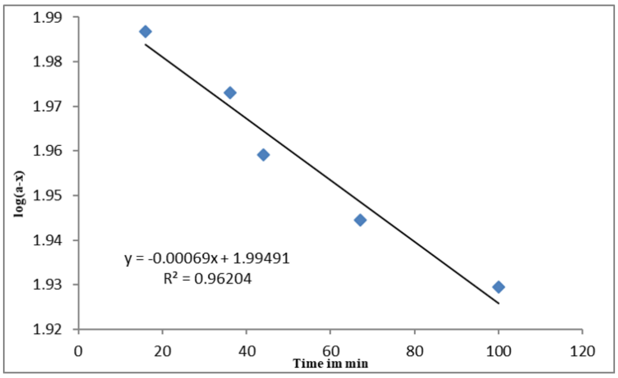


Figure 1: Plot of log(a-x) versus time at 35 °C and periodate (0.002 M), POE (0.025 M) and hydroxide (0.1 M)

Logarithmic values of rate constants were plotted

Table 1: Rate constants in the variation of reaction parameter values

$[KIO_4]$ M	[POE] M	[Alkali] M	Temp (^{0}C)	$k_1 \times 10^4$ min^{-1}
0.00025	0.025	0.1	35	16.78
0.0005	0.025	0.1	35	16.42
0.0010	0.025	0.1	35	15.50
0.0020	0.025	0.1	35	14.67
0.0005	0.0025	0.1	35	16.94
0.0005	0.0125	0.1	35	17.15
0.0005	0.025	0.1	35	16.42
0.0005	0.050	0.1	35	17.99
0.0005	0.100	0.1	35	16.77
0.0005	0.025	0.05	35	18.20
0.0005	0.025	0.1	35	16.42
0.0005	0.025	0.2	35	11.36
0.0005	0.025	0.5	35	7.74
0.0005	0.025	0.1	35	16.42
0.0005	0.025	0.1	40	35.63
0.0005	0.025	0.1	45	55.27
0.0005	0.025	0.1	50	63.90

against logarithmic values of variant concentration, and the slope was used to determine the respective reaction order in the case of POE and hydroxide ion concentrations. Changed the substrate (POE / PEG-300) concentration from 0.0025 to 0.1 M and measured the reaction rates. It was found to be the reaction rate is independent of substrate concentration. Hence, the order was zero in the case of [POE] whereas, substrate inhibition was reported in the literature in the oxidation of different sugar alcohols under similar reaction conditions (Kumar *et al.*, 2014).

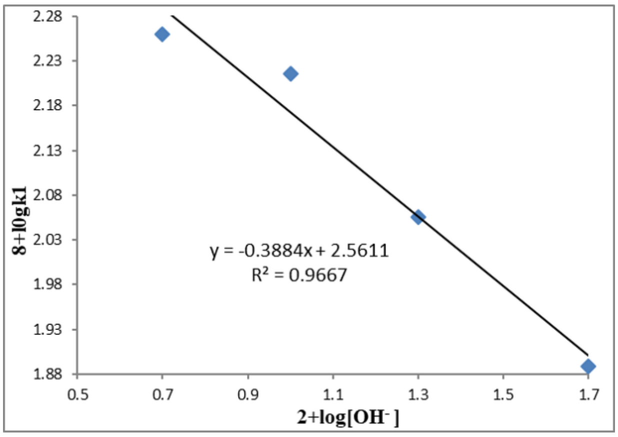
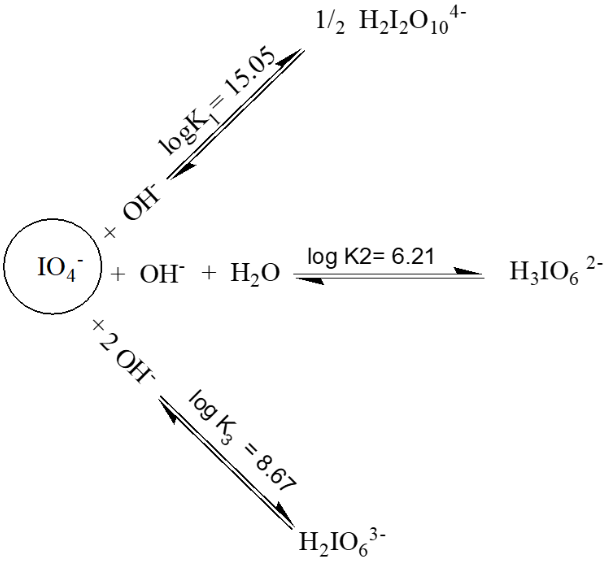


Figure 2: Alkali effect on the rate of oxidation of POE

Alkali concentration effect on the reaction rate was studied by increasing its concentration from 0.05 to 0.5 M. Retardation of rate was observed, which indicates the inverse nature of the reaction. As the slope value was less than one (−0.388) in the plot of log k_1 vs log $[OH^-]$ (Figure 2), inverse fractional order in alkali concentration was concluded.

Equilibrium exists between potassium periodate and its dissociation products in alkaline medium (Aveston, 1969). Equations (1–3) along with concerned equilibrium constants (at 298.2 K) are given below.



Under these equilibrium conditions, the extent of periodate species availability in aq. alkaline conditions can be calculated. At the maintained [OH$^-$] $[IO_4^-]$, and $[H_2I_2O_{10}^{4-}]$are insignificant among the possible four periodate species, whereas, higher concentrations are observed for $[H_3IO_6^{2-}]$ and $[H_2IO_6^{3-}]$ (i.e., species – 3 and 4). In a similar line to other researchers (Tuwar *et al.*, 1992; Shan *et al.*, 2005; Kulkarni and Nandibewoor, 2006), the concentrations of these two predominant species can be calculated by taking the help of Crouthamel *et al.* (1951). $[IO_4^-]_{ex}$ denotes the total concentration of periodate and is considered as equivalent to the sum of$[H_3IO_6^{2-}]$ and $[H_2IO_6^{3-}]$. Based on the two equilibrium conditions (2) and (3), (Shan *et al.*, 2009) has proposed two Equations (4) and (5).

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

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

In molar units, hydroxide concentrations (corresponding $[H_3IO_6^{2-}]$ & $[H_2IO_6^{3-}]$) are 0.025 (0.000107 & 0.000364), 0.05 (0.000180 & 0.000308), 0.10 (0.000267 & 0.000228), 0.20 (0.000349 & 0.000149) and 0.50 (0.000427 & 0.000073). It shows a simultaneous increase in $[H_2IO_6^{3-}]$and decrease in $[H_3IO_6^{2-}]$ with an increase in [OH$^-$]. These two predominant periodate species complex with POE-300.

Activation parameters

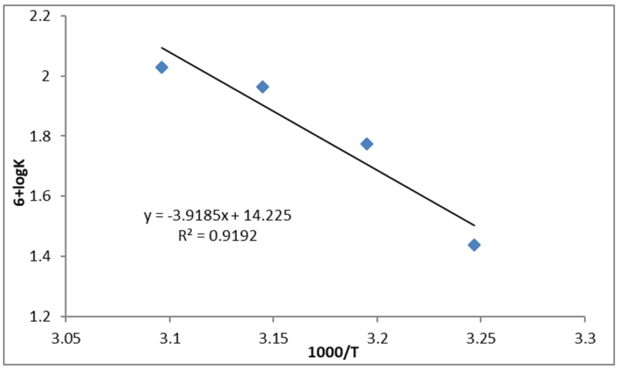


Figure 3: Effect of temperature on rate reaction

Studied the effect of temperature on the reaction rate by measuring first-order constants (k$_1$) at 35, 40, 45 and 50 ^{o}C. Values of k$_1$ increased with an increase of temperature. Least squares method was applied to the plot of log k$_1$ versus 1/T (Figure 3). Eyring equation (Wynne-Jones and Eyring, 1935) was used to determine activation parameters and the values are presented in Table 2.

$$(\Delta\mathbf{E}^{\neq},\ \Delta\mathbf{H}^{\neq},\ \Delta\mathbf{G}^{\neq}\ \text{and}\ -\Delta\mathbf{S}^{\neq})$$

Effect of added boric acid and salts

Kumar *et al.* (2012, 2014) studied the effect of boric acid presence on sugar alcohols oxidation by periodate in alkaline medium. The increased reaction rate was attributed to a favourable environment for the formation of a complex between borate ion and sugar alcohols, which contributes to the substrate inhibition. But no appreciable effect of boric acid is noticed in the present case (Table 3). It can be explained taking into consideration of the presence of more hydroxyl groups on POE (PEG-300) as its hydoxyl value ranges between 340 and 394 (html link). Though, some of the hydroxyl groups of POE complex with borate ions, a good number of free –OH will be available on the substrate. Inclusion of bromide ions increased the reaction rate, but in the contrary, a retarded reaction rate was observed with the other two halide ions (chloride, iodide).

Effect of solvent

To study the effect of solvent on the reaction rate, the reaction was carried out at different proportions of t-butyl alcohol and water (Table 4). The addition of t-butyl alcohol reduced the rate of reaction, indicating that a decrease in the dielectric constant of the medium reduces the reaction rate.

Rate law equation

Long-chain Carboxylic acids were the minor products along with aldehydes as the prime reaction products in the oxidation of POE by periodate in alkaline medium. Spot tests were used to detect so formed products (Feigl, 1956). Aldehydes formation in the present study was further confirmed by converting to 2,4-dinitrophenyldrazones. Szymansi *et al.* (2015) reported the products with the same nature. It shows that terminal –OH groups are active, which corroborates with the common name of these substrates as 'polyethylene glycols' (Henning, 2001). Moreover, its hydroxyl value is practically high. So, the observed final products can be understood from terminal –OH groups oxidation. However, stoichiometry was unable to determine accurately. Derived a suitable rate law as given below, by considering the reactions orders in oxidant, substrate and alkali.

Table 2: Arrhenius parameters at 308 k

Δ**E**$^{\neq}$ KJ/mole	Δ**H**$^{\neq}$ KJ/mole	Δ**S**$^{\neq}$ JK^{-1} / mole	$\log_{10}$ P$_Z$	Δ**G**$^{\neq}$ KJ/mole
75.02	72.46	97.34	8.16	102.44

Table 3: Reaction rate variation with salt concentration

Salt	[Salt] M	k$_1$ x 10^4 min^{-1}
Nil	Nil	16.42
KCl	0.1	12.80
KBr	0.1	25.71
KI	0.1	4.29
KNO_3	0.1	15.90
Boric Acid	0.01	15.43
Boric Acid	0.025	14.91
Boric Acid	0.05	15.80

[periodate] = 0.0005 M [POE] = 0.025 M
Temperature= 35^{o}C [OH$^-$] = 0.1 M

Table 4: Effect of solvent

t-butyl alcohol : water (v/v)	k$_1$ x 10^4 min^{-1}
0 : 100	16.42
5 : 95	6.98
10 : 90	6.56
20 : 80	6.68
40 :60	6.63

C$_1$ and C$_2$ are the complexes formed between the substrate (POE) and the active species -of periodate ($[H_3IO_6^{2-}]$ and $[H_2IO_6^{3-}]$). Then the products are formed by rate-determining dissociation of these complexes.

$$Species-3\ +\ S\ \overset{k_4}{\leftrightarrows}\ Complex\ C_1\ \xrightarrow{k_1}\ Products$$
$$Species-4\ +\ S\ \overset{k_5}{\leftrightarrows}\ Complex\ C_2\ \xrightarrow{k_2}\ Products$$

Rate = k$_1$ [C$_1$] + k$_2$ [C$_2$] = $[IO_4^-]$ [OH$^-$] [S] {k$_1$K$_2$K$_4$ + k$_2$K$_3$K$_5$[OH$^-$]}

Out of$[IO_4^-]$,$H_2I_2O_{10}^{4-}$, $H_3IO_6^{2-}$, $H_2IO_6^{3-}$, Complex C$_1$ and Complex C$_2$, the first two species are negligible, overall periodate concentration, $[IO_4^-]_T$ is rewritten as given below.

$[IO_4^-]_T$ = [species-3] + [species-4] + [C$_1$] + [C$_2$]

As the hydroxyl values of POE (PEG-300) is in the range of 340-394 (html link), a large number of –OH are available and hence, species-3 and species-4 are completely complexed with them. Therefore, concentrations of those two species can be neglected to rewrite the above equation as

$[IO_4^-]_T$ = [C$_1$] + [C$_2$] = K$_2$ K$_4$ [S] $[IO_4^-]$ [OH$^-$] + K$_3$K$_5$ [S] $[IO_4^-]$ [OH$^-$]^2

The above equation can be rearranged to get

$$[IO_4^-]\ =\ \frac{[IO_4^-]_T}{[OH^-][S]\ \{K_2\ K_4\ +\ K_3\ K_5\ [OH^-]\ \}}$$

By substituting the value of $[IO_4^-]$ in the rate expression, we can conclude that

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

The above rate law explains the observed reaction orders (first order in [oxidant] and independence of reaction to [substrate]). In comparison to the denominator, the value of [OH$^-$] value in the numerator is small due to k$_2$<<1. And hence, inverse fractional order in [OH$^-$] can be explained.

CONCLUSION

Periodate oxidation of POE (or PEG-300, a key polymer in the pharmaceutical industry) followed first order kinetics in [oxidant], independent of [substrate] and inverse fractional order in [OH$^-$]. Postulated a suitable rate by considering the experimental results.

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