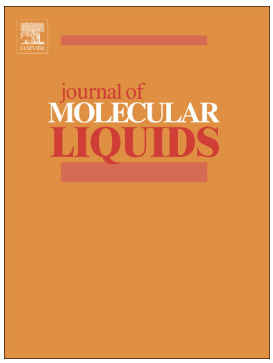

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PII: S0167-7322(20)32621-0

DOI: https://doi.org/10.1016/j.molliq.2020.113963

Reference: MOLLIQ 113963

To appear in: *Journal of Molecular Liquids*

Received date: 26 April 2020

Revised date: 16 July 2020

Accepted date: 30 July 2020

Please cite this article as: F. Rahman, M.S. Ali, H.A. Al-Lohedan, et al., Influence of PVP-PEG mixed aggregates and electrolytes on the rate of alkaline hydrolysis of benzocaine in aqueous and surfactant medium, *Journal of Molecular Liquids* (2018), https://doi.org/10.1016/j.molliq.2020.113963

Influence of PVP-PEG mixed aggregates and electrolytes on the rate of alkaline hydrolysis of benzocaine in aqueous and surfactant medium

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ABSTRACT

The present work describes the effects of the interactions between the two water-soluble polymers poly(vinyl pyrrolidone) (PVP) and poly(ethylene glycol) (PEG) on the rate of the alkaline hydrolysis of benzocaine. The roles of the surfactants cetyltrimethylammonium bromide (CTABr) and sodium dodecyl sulfate (SDS) in the binding of benzocaine with PVP-PEG mixed systems has also been explored through changes in the reaction rate. Our results revealed that the reaction rate decreases with the increasing [PVP] when [PEG] is fixed. Similarly, the rate of hydrolysis also decreases on increasing [PEG] while [PVP] is fixed. The combined rate constant values for the hydrolysis of benzocaine in the aqueous and mixed PVP-PEG system (k_Ψ) increases with increasing [CTABr] in the lower concentration range, then decreases with further increase in [CTABr], giving a peaked profile for k_Ψ vs. [CTABr]. The increase in [SDS] in the mixed PVP-PEG system decreases the rate of hydrolysis. Accordingly, the observed results show that the binding constant values (i.e., the degree of association) of benzocaine with PVP-PEG in the presence of CTABr and SDS are lower. Furthermore, increasing the molecular weight of PEG in the surfactant-PVP-PEG complex decreases the binding constant values of the benzocaine-polymer complex due to the formation of less compact aggregates. The effects of electrolytes (CH_3COONa, NaCl, Na_2SO_4, and$NaNO_3$) were also investigated, and they were found to decrease reaction rate.

Keywords: benzocaine; alkaline hydrolysis; poly(vinyl pyrrolidone); poly(ethylene glycol); surfactant-PVP-PEG aggregate

1. INTRODUCTION

The presence of soluble hydrophilic polymers and surfactants in aqueous reaction media have remarkable effects on the properties of the solution due to the formation of associative structures [1]. Their presence in such aqueous solutions leads to wide variations in microstructure, viscosity, and surface tension properties that, in turn, influence the rate of reactions therein [2-6]. Polymer-polymer and polymer-surfactant interactions cause changes in the polarity of the solution medium as well as the microstructure of the reaction medium. These factors affect the binding ability of the reactive molecules with the polymer-polymer and polymer-surfactant aggregates. The influence of surfactants on the reactivities of organics has been the subject of studies for many decades. In most of these studies, it was observed that cationic surfactants initially increase the hydrolysis rates of carboxylic and carbonate esters, followed by a rate decrease beyond a certain surfactant concentration, while anionic surfactants simply decrease the rate of hydrolysis, irrespective of concentration [7].

When polymer and surfactant are present in a reaction medium, they complement each other's properties [8]. The extent of the interactions between the polymer and surfactant molecules influence solution properties, such as viscosity and surface tension, and depends upon their nature and mixing ratio [9, 10]. The ability of the polymer and surfactant to alter the reaction rate varies according to the state of their aggregation in the aqueous solution phase, i.e., the nature of the interactions between them [2-5]. The two possible modes of polymer-surfactant interaction are (i) the direct association or binding of the surfactant with the polymer, and (ii) the micellization of the surfactant on or near the polymer chain [11]. The factors influencing the polymer-surfactant association include the hydrophobicities of the polymer and surfactant, their ionic (or non-ionic) nature, and the presence of additives [12, 13]. The addition of an ionic surfactant to an aqueous solution of an uncharged polymer leads to a hydrophobic interaction between the polymer and the hydrophobic part of the surfactant, making the surfactant thermodynamically compatible with the hydrophobic part of the polymer [12]. From an application standpoint, their mixture can produce enhanced effects such as Gemini surfactant/conjugated polymer aggregates that have been demonstrated to enhance fluorescence and thus provide bio-imaging capabilities [14] and also enhance the chemo-therapeutic activity of doxorubicin [15].

The alkaline hydrolysis of several anesthetic drugs, such as benzocaine [2], tetracaine [3], and procaine [4, 5] has been studied in aqueous and surfactant-poly(ethylene glycol) (PEG)

media. The rates of hydrolysis of procaine and tetracaine are suppressed by the presence of surfactants, and the subsequent addition of PEG shows further inhibitory effects which, in turn, lead to an increase in the stability of these drugs. A slightly different behavior was observed for benzocaine in the presence of cetyltrimethylammonium bromide (CTABr), where a peak is observed in the plot of rate constant vs. [CTABr] [2]. Poly(vinyl pyrrolidone) (PVP) has an inhibitory effect on the alkaline hydrolysis of benzocaine, but single-peaked and double-peaked behavior is observed for PVP-CTABr and PVP-sodium dodecyl sulfate (SDS) mixed media, respectively [16].

Owing to the promising properties of systems containing polymer-polymer and surfactant-polymer mixtures, investigating the effect of such systems on the rate of reactions therein is a worthwhile research undertaking. Accordingly, we have selected the alkaline hydrolysis of the well-known drug benzocaine as a model system. Changes in reaction rate in the presence of polymer mixtures, polymer-surfactant aggregates, and polymer-electrolyte aggregates are the direct consequence of changes in the properties of the reaction medium and the association behavior of benzocaine with the polymer aggregates. The kinetic method can serve as a simple technique for determining the solution microstructure, state of polymer aggregation (in the presence of other polymers, surfactants, and electrolytes), and the ability of polymer-surfactant aggregates to bind and carry organic molecules.

In the present investigation, the effects of a binary polymer system (PEG and PVP) and their aggregated structures on the rate of alkaline benzocaine hydrolysis in the absence and presence of surfactants have been studied. Additionally, the effect of electrolytes on reaction kinetics was also investigated. The changes in the rate of reaction have been explained by considering the pseudophase model and pseudophase ion-exchange model. The application of these models was found to successfully rationalize the distribution patterns of benzocaine and hydroxide ions in the aqueous and polymer-surfactant aggregates.

2. EXPERIMENTAL

2.1. Materials

PEG (average molecular weights of 1500, 4000, 6000, and 8000 Da) and PVP (K-30; average molecular weight of 40,000 Da) were purchased from CDH, New Delhi, India. Benzocaine (~99% purity) was obtained from Himedia, Mumbai, India. Sodium hydroxide pellets (~97% purity) was supplied by Merck, Mumbai, India. CTABr (~99% purity) and SDS (~99%

purity) were obtained from CDH, New Delhi, India. All the reagents were of analytical grade and used without further purification. Ethanol was used as a solvent to prepare a stock solution of benzocaine (5.0×10^{-3} mol dm^{-3}). Double-distilled water was used to prepare stock solutions of surfactant (1.0×10^{-1} mol dm^{-3}), the PEGs (5%; *w/v*), PVP (5%; w/v), and NaOH (1.0×10^{-1} mol dm^{-3}).

2.2. Spectroscopic measurement

Spectroscopic analyses were performed on a Genesys10S double-beam spectrophotometer (Thermo Fisher, Madison, USA) by monitoring the absorption intensity of benzocaine at 284 nm (λ_{max}). The spectra of the samples containing benzocaine in PVP-PEG mixtures were recorded in the absence and presence of surfactants. The temperature of the reaction mixtures was maintained constant at 40.0 ± 0.2 °C using a Ferrotek thermostat (Ghaziabad, India). Pseudo-first-order reaction conditions (i.e., [NaOH]>>[Benzocaine]) were maintained for all kinetics measurements. The reactions were initiated by the addition of the requisite amount of NaOH to the reaction flask containing a pre-equilibrated reagent solution of benzocaine, PEG, PVP, and surfactants. The spectra of the samples were recorded using a 3-mL quartz cuvette every 5 min. The progress of alkaline benzocaine hydrolysis was monitored by reference to the decrease in absorbance at 284 nm and the simultaneous appearance of a new peak at 266 nm. The reactions were followed to approximately 80% completion. Pseudo-first-order rate constants (k, s^{-1}) were calculated from the slopes of the plots of ln (absorbance) vs. time. Each set of experiments was performed in triplicate to ensure the reproducibility of the rate constant values within the minimum percentage random error (± 5%).

3. RESULTS AND DISCUSSIONS

3.1. Hydrolysis of benzocaine in PVP-PEG aggregate

The repeated analyses of a benzocaine solution (3.0×10^{-5} mol dm^{-3}) containing PVP (8.0×10^{-6} mol dm^{-3}), PEG 1500, (6.0×10^{-6} mol dm^{-3}), and NaOH (5.0×10^{-2} mol dm^{-3}) were recorded at a uniform interval of 5 min and 40.0 ± 0.2 °C (Fig. 1). The formation of an isosbestic point in the spectra indicate the involvement of only two species in the reaction, i.e.,benzocaine and p-aminobenzoate anions, which are responsible for the change in absorption intensity about the isosbestic point. The alkaline hydrolysis of benzocaine causes a decrease in absorbance intensity at 284 nm, while formation of the hydrolysis product p-amino-benzoate anion causes an increase in absorbance at 266 nm as the reaction progresses

[2].

The basic hydrolysis of benzocaine was studied for different [NaOH] values while keeping [benzocaine] (3.0×10^{-5} mol dm^{-3}), [PVP] (8.0×10^{-6} mol dm^{-3}), and [PEG] (6.0×10^{-6} mol dm^{-3}) constant for all four molecular weights of PEG (1500, 4000, 6000, and 8000).The rate constant vs. [NaOH] (Fig.2) plots show linear relationships for all the variants of PEG used. The alkaline hydrolysis of benzocaine proceeds by the nucleophilic attack of OH^- ions on the electron deficient carbonyl carbon of the benzocaine molecule, creating a tetrahedral intermediate. The intermediate-generation step is considered to be the rate governing step of the reaction. The intermediate formed is highly unstable and degrades immediately into p-amino-benzoate and ethoxide as the final reaction products.

To study the influence of PVP-PEG aggregates on reaction rate, kinetics experiments were carried out for PVP-PEG mixed systems with different PVP to PEG ratios. Figure 3 shows the plots for rate constant vs. [PVP] taken in the range 2.0×10^{-6}–10.0×10^{-6} mol dm^{-3} in the presence of [PEG] (6.0×10^{-6} mol dm^{-3}) and fixed [benzocaine] (3.0×10^{-5} mol dm^{-3}), and [NaOH] (5.0×10^{-2} mol dm^{-3}). The rate of hydrolysis decreases with increasing [PVP] in the presence of PEG.

The effect of varying [PEG] in the presence of PVP on the reaction rate was studied for the [PEG] range 2.0×10^{-6} mol dm^{-3} to 10.0×10^{-6} mol dm^{-3} keeping [benzocaine] (3.0×10^{-5} mol dm^{-3}), [PVP] (8.0×10^{-6} mol dm^{-3}), and [NaOH] (5.0×10^{-2} mol dm^{-3}) constant (Fig. 4). Again, the rate constant decreases with increasing PEG concentration in PVP-PEG mixed systems. The PVP and PEG molecules present in the aqueous medium are thought to form intermolecular complexes. The proton-donor hydroxyl group present at each end of the PEG chain creates a hydrogen bond with the proton-accepting carbonyl groups present in the PVP molecules [17, 18]. Scheme 1 depicts the binding of the benzocaine molecules within and around the PVP-PEG aggregate structure. Thus, PEG chains are considered to act as hydrogen-bonded crosslinks between the bulky PVP chains, forming voids that host the benzocaine molecules through hydrophobic or electrostatic interactions. As the concentration of PVP in PVP-PEG increases, the complexity of the PVP-PEG aggregation increases. The reactants, i.e., benzocaine and OH^- become segregated into different pseudophases (i.e., the PVP-PEG complex phase and the aqueous phase) and, thus, the rate of reaction decreases. The PEG molecules in the PVP-PEG mixed solution also act as water-structure breakers and compete with the water molecules associated with the PVP chains to form hydrogen bonds

with PVP. Thus, with increasing [PEG] in the PVP-PEG mixture, the association of the hydroxyl group of PEG with the carbonyl group of PVP increases by the replacement of the water molecules directly associated with the PVP chains, forming denser complexes. As a result, the concentration of OH^- ions around the PVP-PEG complexes encapsulating the benzocaine molecules starts decreasing and, thus, the rate of the reaction decreases. The rate of reaction is found to be higher for the higher-molecular-weight PEGs (4000, 6000, 8000) than for the low-molecular-weight PEG (1500). The repulsive intermolecular interaction between the PVP and PEG is increased by increasing the molecular weight of PEG. Furthermore, an increase in the molecular weight of PEG increases the number of hydroxyl groups in and around the PEG and, thus, increases its hydrodynamic volume. An increase in hydration number in and around the PEG and PVP complex will decrease the hydrogen bonding between PVP and PEG. This leads to a repulsive interaction between PVP and PEG molecules and thus the formation of less compact aggregates for hosting the benzocaine molecules. The concentration of OH^- ions is comparatively higher due to the increased hydration number in these less-compact high-molecular-weight PEG complexes. Therefore, the rates of reaction are higher in the presence of high-molecular-weight PEG. Denser complexes are formed with low-molecular weight PEG and PVP owing to the lower hydration number and, hence, the reaction rates are lower. Scheme 1 depicts the association of PEG-PVP with benzocaine.

3.1 Hydrolysis of benzocaine in ternary PVP-PEG-surfactant media

The kinetics of the alkaline hydrolysis of benzocaine in ternary systems composed of surfactant (CTABr or SDS) and two hydrophilic polymers (PVP and PEG) were studied. The hydrolysis rates of [benzocaine] (3.0×10^{-5} mol dm^{-3}) in CTABr-PVP-PEG mixed medium at constant [PVP] (8.0×10^{-6} mol dm^{-3}), [PEG] (6.0×10^{-6} mol dm^{-3}), and [NaOH] (5.0×10^{-2} mol dm^{-3}) were studied with [CTABr] from 1.0×10^{-3} mol dm^{-3} to 16.0×10^{-3} mol dm^{-3}.The combined aqueous-and micellar-pseudophase rate constant (k_Ψ) vs. [CTABr] (Fig.5) plots show an initial increase in the rate constant with the peak value at 2.0×10^{-3} mol dm^{-3} followed by a decrease with further increase in [CTABr].

The SDS-PVP-PEG interaction was investigated by studying the rate of alkaline hydrolysis of benzocaine (3.0×10^{-5} mol dm^{-3}) in a medium with fixed [PVP] (8.0×10^{-6} mol dm^{-3}), [PEG] (6.0×10^{-6} mol dm^{-3}), and [NaOH] (5.0×10^{-2} mol dm^{-3}) and with [SDS] in the range from 1.0×10^{-3} mol dm^{-3} to 16.0×10^{-3} mol dm^{-3}. The plot for k_Ψ - SDS (Fig. 6) shows a

decreasing trend in rate constant with increasing [SDS]. The various phases formed in the ternary system, i.e., the aqueous phase, the surfactant-PVP-PEG ternary aggregate phase, and the surfactant phase, have the capability to solubilize the benzocaine molecule and hence alter the reaction rate to different extents. Based on this assumption, a reaction mechanism for the alkaline hydrolysis of benzocaine in a ternary surfactant-PVP-PEG system is proposed and presented in Schemes2 and 3 [3].

The overall reaction occurring in the presence of surfactant-PVP-PEG is presented in Scheme 4. The rate equation for the alkaline hydrolysis of benzocaine in ternary surfactant-PVP-PEG medium is given by Eq. 1 [2-4],

$$\text{Rate} = k'_w [S_w] + k'_p [S_p] + k'_m [S_m] \quad (1)$$

where, $[S_w]$, $[S_p]$,and $[S_m]$ represent the concentration of benzocaine in the aqueous, surfactant-PVP-PEG, and surfactant pseudophases, respectively. k'_w , k'_p and k'_m represent the first-order rate constant for the aqueous, surfactant-PVP-PEG, and surfactant pseudophases, respectively.

The maxima behavior of the rate constant in CTABr-PVP-PEG ternary system is thought to be a consequence of the intermolecular associations among the molecules of CTABr, PVP, and PEG in the aqueous medium. Furthermore, this observation is in accordance with previous findings on the hydrolysis of benzocaine in the presence of CTABr alone [2]. In the pre-micellar region, the rate of benzocaine hydrolysis increases within creasing [CTABr], which further indicates the repulsive interaction between the benzocaine-holding cationic CTABr molecules and the slightly positively charged PVP molecules. The PEG molecules added form hydrogen bonds with PVP. Hydrophobic interactions and hydrogen bonding along the polymer segments result in the formation of a denser PVP-PEG complex. The repulsive interactions for the complex modify the water activity around its surface region. In the presence of CTABr, the hydration level of PVP-PEG is increased, increasing the local concentrations of benzocaine and OH^- ions. Thus, the rate of hydrolysis is increased. Furthermore, some free surfactant molecules form complexes with the hydrophobic segments of the PVP-PEG complex globules upon an increase in surfactant concentration. In the post-micellar region, the self-associated CTABr structures are thought to form intermolecular complexes with PVP and PEG[11, 19], which alter the water-water association in the palisade region. The surfactant micelles formed near the PVP-PEG complexes are trapped in the chains of PVP-PEG[2],which results in the shielding of benzocaine molecules enclosed in

surfactant micelles. This leads to a decrease in reactant (benzocaine and OH^-) interactions and collisions, and hence a drop in the reaction rate is observed.

A cursory look at the decreasing trend in the reaction rate for the ternary SDS-PVP-PEG system might lead one to consider the intermolecular complexes formed between the surfactant and polymers. At lower [SDS], the surfactant monomers holding the benzocaine molecules by hydrophobic interaction are thought to be drawn together by the more hydrophobic PVP polymer (as compared to PEG) to form clusters. Some of the PVP chain surrounds the benzocaine-associated SDS monomers with its polar-carbonyl-containing head-groups in the outer region. The PEG added to the mixture will envelope the SDS-PVP aggregates due to hydrogen bonding between the hydroxyl group of PEG and the carbonyl group of PVP. This changes the polarity and, hence, lowers the water activity in and around the surface region of the SDS-PVP mixed aggregates containing benzocaine. The decrease in hydration number around the SDS-PVP aggregates decreases the concentration of OH^- ions, and therefore the rate of benzocaine hydrolysis decreases [6]. Upon further increase in [SDS], the SDS monomers start aggregating and eventually form micelles beyond their critical micelle concentration with PVP and PEG [20, 21]. Concurrently, the benzocaine molecules continue to lose contact with the OH^- ions due to poor water activity in the mixed aggregates/ palisade layer of the PVP-PEG. Hence, the rate of alkaline hydrolysis of benzocaine decreases with increasing [SDS] in ternary SDS-PVP-PEG systems.

The presence of polymer(s) in the micellar media lowers the surface tension between the surfactant micellar core and water, resulting in a stabilized interface between them. This is also considered to be a significant reason for the interaction among the surfactants and polymers (beside the interactions occurring due to the presence of their different functional groups) [1]. As a result, very few surfactant micelles are assumed to be in the unbound state, and the hydrolysis reaction is considered to be chiefly occurring in the aqueous and surfactant- PVP-PEG phases. Consequently, the terms for the surfactant pseudophase in Eq. 1 can be omitted and the final equation takes the form of Eq. 2:

$$\text{Rate} = k'_w[S_w] + k'_p[S_p] \qquad (2)$$

$[OH^-]$ in the vicinity of CTABr in the CTABr-PVP-PEG mixed aggregates has been quantified using the pseudophase ion-exchange model, in which the Br^- ions on the micellar surface are substituted by OH^- ions as counterions. Based on the equilibrium constants and the $[OH^-]$ involved in the exchange model, Eq. 2 can be rewritten as Eq.3 in order to obtain the kinetic parameters k_p and K_B for a ternary CTABr-PVP-PEG system [2-4].

$$k_{\psi} = \frac{k_2[OH_T^-] + (k_p K_B - k_2) m_{OH}[PD_n]}{1 + K_B[PD_n]} \quad (3)$$

The kinetics of the reaction taking place in the SDS-PVP-PEG system have been derived quantitatively using the pseudophase model, which assumes the partition of the reacting species (here benzocaine and OH^- ions) between different pseudophases. The benzocaine is assumed to remain in the SDS-PVP-PEG phase, while the OH^- ions concentrate predominantly in the aqueous phase. Rearrangement of Eq. 2 yields Eq. 4, which has been used to calculate k'_w, k'_p, and K_p for a reaction occurring in an SDS-PVP-PEG system.

$$\frac{1}{k'_w - k_{\psi}} = \frac{1}{k'_w - k'_p} + \frac{1}{(k'_w - k'_p) K_B [PD_n]} \quad (4)$$

Here, K_B is the binding constant of benzocaine with surfactant-PVP-PEG aggregates; $[PD_n]$ is the concentration of surfactant – PVP - PEG aggregates; and k'_p represents the first-order rate constant for the reaction occurring in the surfactant-PVP-PEG pseudophase.

The results obtained for the binding constant of benzocaine with a surfactant-PVP-PEG aggregate show a decreasing trend with an increase in the molecular weight of PEG (Tables 1 and 2), while the micellar rate constants are found to increase with an increase in PEG molecular weight (Tables 1and 2).The ternary complexes formed in the presence of low-molecular-weight PEGs are more compact and stronger (due to hydrogen bonding between PVP and PEG) [22, 23] than those formed by high-molecular-weight PEGs (which favor intermolecular repulsive interaction between PVP and PEG). The benzocaine molecules are thus assumed to be more strongly associated with the surfactant through hydrophobic interaction in the compact ternary complexes of low-molecular-weight PEGs, resulting in high binding constant values. Furthermore, the compactness of the complexes decreases the probability of the reactants (benzocaine and OH^- ions) interacting, resulting in a decreased reaction rate. As a result, the micellar rate constants are lower in ternary complexes with low-molecular-weight PEGs.

3.3. Effect of electrolytes on the hydrolysis of benzocaine in PVP-PEG aggregates

Electrolytes have a large, and somewhat unusual, impact on the rates of reactions catalyzed by the presence of aggregates. A reactive salt can cause a rate enhancement while an inert salt may inhibit the reaction by displacing the reactants and disrupting their contact. Numerous studies on the effects of salts in the micellar pseudophase have been reported in the literature [24]. In this study, we also investigated the effects of several salts (CH_3COONa, NaCl,

Na_2SO_4, $NaNO_3$, KBr, and KCl) on the rate of benzocaine hydrolysis in a PEG-PVP pseudophase. The plots of rate constant (k) vs [Electrolyte] in presence of fixed amounts of NaOH, PVP, and PEG (of various molecular weights) with varying amounts of electrolyte are given in Fig. 7. All the electrolytes used in the present study were found to inhibit the rate of hydrolysis of benzocaine in PVP-PEG medium. From the cumulative information given in Fig. 7 for all molecular weights of PEG, the order of inhibition is $SO_4^{2-} > Cl^- > CH_3COO^- > NO_3^-$. There is no apparent difference between the inhibitory effects of KCl, KBr, and NaCl. The addition of an inert electrolyte (CH_3COONa, NaCl, $NaNO_3$, and Na_2SO_4) to the PVP-PEG medium decreases the concentration of OH^- ions in the domain of the polymer complexes due to its competition with the counter anions (CH_3COO^-,Cl^-, NO_3^-,and SO_4^{2-}) present in the aqueous phase of the medium. As a result, the probability of reactant interaction decreases with an increase in electrolyte concentration, decreasing the reaction rate. Collectively, it can be deduced that all inert electrolytes show an inhibitory effect and can be used in combination with polymers to increase the stability of the drug.

4. CONCLUSION

The neutral water-soluble polymers PVP and PEG, when present in aqueous media, exhibit a tendency to form complexes through intermolecular interactions. The PEGs are thought to crosslink with bulky PVP chains through hydrogen bonding. The voids formed in such complexes host the benzocaine molecules through electrostatic/hydrophobic interactions. The varied complexity of these aggregates plays an important role in altering the rates of reaction. The morphology of a PVP-PEG aggregate is concentration-dependent. The complexity of these aggregates increases with increasing [PVP] and [PEG], which results in a decrease in reaction rate. In the pre-micellar concentration region of CTABr, less compact aggregates of CTABr-PVP-PEG are formed due to repulsive interaction between CTABr and PVP molecules, which results in an increase in reaction rate. However, in the post-micellar concentration region, the CTABr micelles become entrapped in the PVP-PEG chains, forming compact aggregates that hinder benzocaine hydrolysis. The SDS-PVP clusters formed in the pre- and post-micellar regions due to hydrophobic attraction are covered by PEG molecules through hydrogen bonding between the carbonyl groups of PVP and the hydroxyl groups of PEG. As a result, denser ternary SDS-PVP-PEG complexes are formed with poor water activity, leading to a decrease in hydrolysis rate. Furthermore, the molecular weight of the PEG in the ternary complexes (surfactant-PVP-PEG) plays an important role in their

structure. Complexes formed by low-molecular-weight PEGs are more compact than those formed by high-molecular-weight PEG complexes. Furthermore, inert electrolytes were also found to inhibit the rate of hydrolysis in the presence of PVP-PEG aggregates. Overall, the results of this study will be helpful in designing more stable drug formulations for benzocaine.

Acknowledgments

Farheen Rahman is thankful to the UGC, New Delhi, for the award of a Non-NET fellowship. MSA and HAA are grateful to the Deanship of Scientific Research, King Saud University, for funding through the Vice Deanship of Scientific Research Chairs. The authors thank the Deanship of Scientific Research and RSSU at King Saud University for their technical support.

Conflict of interests:

The authors declare no conflicts of interest.

Author Contribution

Farheen Rahman: Investigation, Formal analysis, Writing – original draft, Writing - review & editing. **Mohd Sajid Ali:**Formal analysis, Writing – original draft, Writing - review & editing. **H.A. Al-Lohedan:** Writing – original draft. **Ghulam Aazam:** Writing – original draft. **Daifallah M. Aldhayan:** Writing – original draft. **M.Z.A. Rafiquee:** Investigation, Formal analysis, Writing – original draft, Writing - review & editing.

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Scheme Captions

Scheme 1. Schematic representation of the interaction between PVP and PEG and their effect on benzocaine segregation

Scheme 2. Aggregated structure of a CTABr-PVP-PEG system in aqueous medium

Scheme 3. Aggregated structure of the SDS-PVP-PEG system in aqueous medium

Scheme 4. Distribution of the reactants in various pseudo-phases

Figure Captions

Fig.1. UV-visible spectra of the benzocaine (3.0×10^{-5} mol dm^{-3}) solution in aqueous medium containing PVP (8.0×10^{-6} mol dm^{-3}), PEG 1500 (6.0×10^{-6} mol dm^{-3}) and NaOH (5.0×10^{-2} mol dm^{-3}), traced at regular time period of 5 minutes at 40.0 ± 0.2°C.

Fig. 2. Plot of rate constant (k) *versus* [NaOH] for the hydrolysis of benzocaine (3.0×10^{-5} mol dm^{-3}) in the presence of PVP (8.0×10^{-6} mol dm^{-3}) and PEG (6.0×10^{-6} mol dm^{-3}) at 40.0 ± 0.2°C.

Fig. 3. Plot for the rate constant (k) *versus* [PVP] for the hydrolysis of benzocaine (3.0×10^{-5} mol dm^{-3}) in the presence of NaOH (5.0×10^{-2} mol dm^{-3}), PEG (6.0×10^{-6} mol dm^{-3}) and PVP (2.0×10^{-6} mol dm^{-3} to 10.0×10^{-6} mol dm^{-3}) at 40.0 ± 0.2°C.

Fig. 4. Plot of the rate constant (k) *versus* [PEG] for the hydrolysis of benzocaine (3.0×10^{-5} mol dm^{-3}) in the presence of NaOH (5.0×10^{-2} mol dm^{-3}), PVP (8.0×10^{-6} mol dm^{-3}) and PEG (2.0×10^{-6} mol dm^{-3} to 10.0×10^{-6} mol dm^{-3}) at 40.0 ± 0.2°C.

Fig. 5. Plot of rate constant (k) *versus* [CTABr] for the hydrolysis of benzocaine (3.0×10^{-5} mol dm^{-3}) in the presence of NaOH (5.0×10^{-2} mol dm^{-3}), PVP (8.0×10^{-6} mol dm^{-3}), PEG (6.0×10^{-6} mol dm^{-3}) and CTABr (2.0×10^{-3}mol dm^{-3} to 16.0×10^{-3} mol dm^{-3}) at 40.0 ± 0.2°C.

Fig. 6. Plot of rate constant (k) *versus* [SDS] for the hydrolysis of benzocaine (3.0×10^{-5} mol dm^{-3}) in presence of NaOH (5.0×10^{-2} mol dm^{-3}), PVP (

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Fig. 7. Plots of rate constant (k) *versus* [Electrolyte] for the hydrolysis of benzocaine (3.0×10^{-5} mol dm^{-3}) in the presence of NaOH (5.0×10^{-2} mol dm^{-3}), PVP (8.0×10^{-6} mol dm^{-3}), PEG (6.0×10^{-6} mol dm^{-3}) with [electrolyte] ranging from 2.0×10^{-3} mol dm^{-3} to 10.0×10^{-3} mol dm^{-3}at 40.0 ± 0.2°C in the presence of PEGs of different molecular weights.

Table 1: Kinetic parameters K_B (binding constant) and k_p (rate constant) derived for the alkaline hydrolysis of benzocaine in ternary CTABr-PVP-PEG mixed systems.

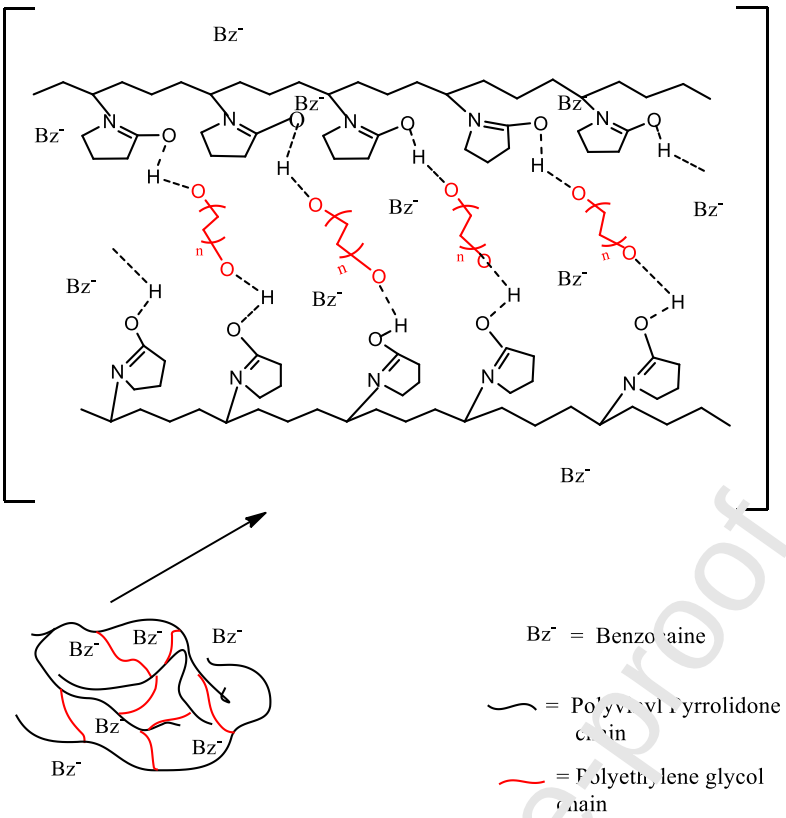
M.W. of PEG	K_B	$10^3 k_p$ (s^{-1})
1500	200	1.89
4000	150	2.04
6000	129	2.12
8000	119	2.28

Reaction conditions: [Benzocaine] = 3.0×10^{-5} mol dm^{-3}, [NaOH] = 5.0×10^{-2} mol dm^{-3}, [PVP] = 8.0×10^{-6} mol dm^{-3} , [PEG] = 6.0×10^{-6} mol dm^{-3}, [CTABr] = 2.0×10^{-3} mol dm^{-3}- 16.0×10^{-3} mol dm^{-3}, Temperature = 40 ± 0.2°C, β=0.8, K^{Cl}_{Br} = 12.

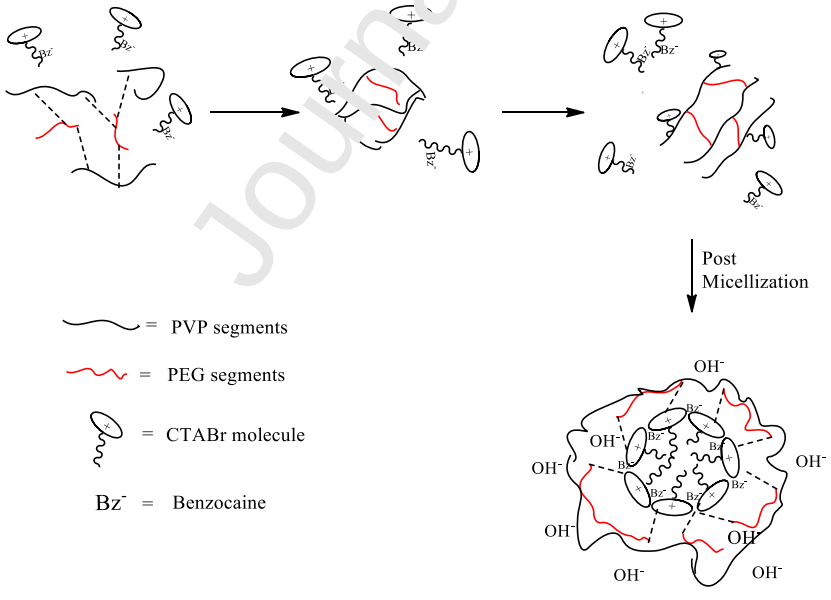
Table 2: Kinetic parameters K_B (binding constant) and k_p (rate constant) derived for the alkaline hydrolysis of benzocaine in SDS-PVP-PEG ternary mixed system.

M.W. of PEG	K_B	$10^3 k_p$ (s^{-1})
1500	60.67	1.07
4000	34.19	1.12
6000	36.25	1.41
8000	39.05	1.74

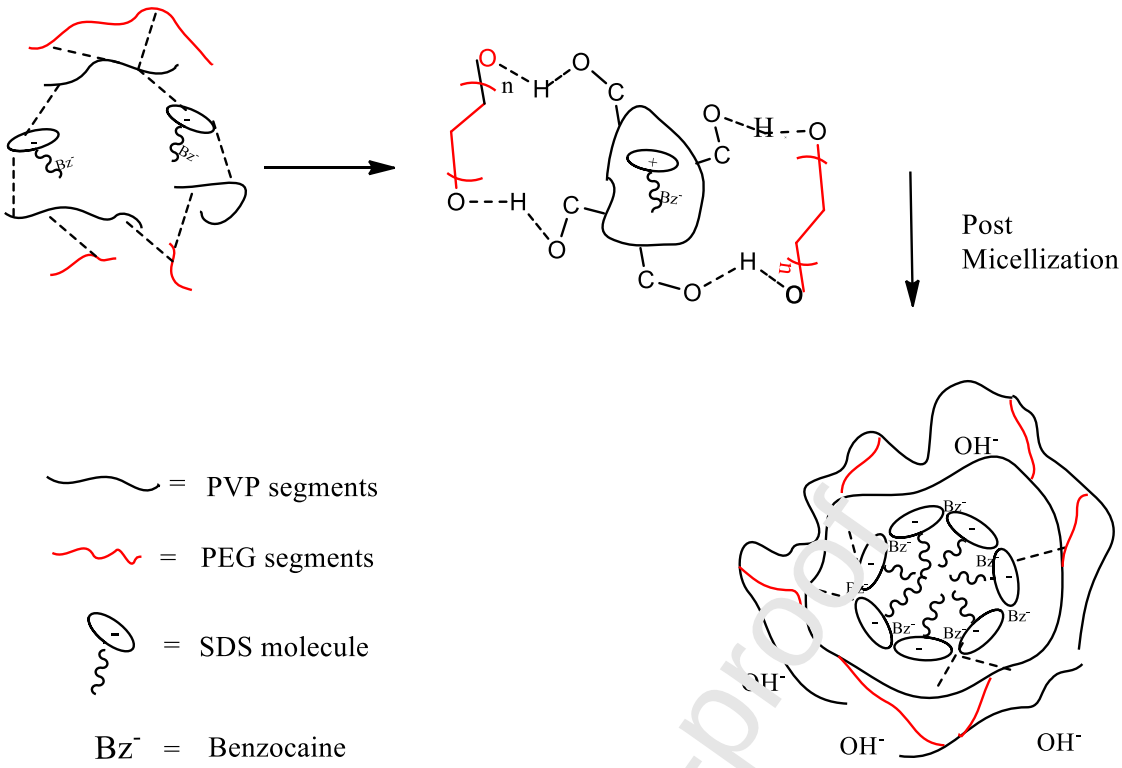
Reaction conditions: [Benzocaine] = 3.0×10^{-5} mol dm^{-3}, [NaOH] = 5.0×10^{-2} mol dm^{-3}, [PVP] = 8.0×10^{-6} mol dm^{-3}, [PEG] = 6.0×10^{-6} mol dm^{-3}, [SDS] = 2.0×10^{-3} mol dm^{-3} - 16.0×10^{-3} mol dm^{-3}, Temperature = 40 ± 0.2°C.



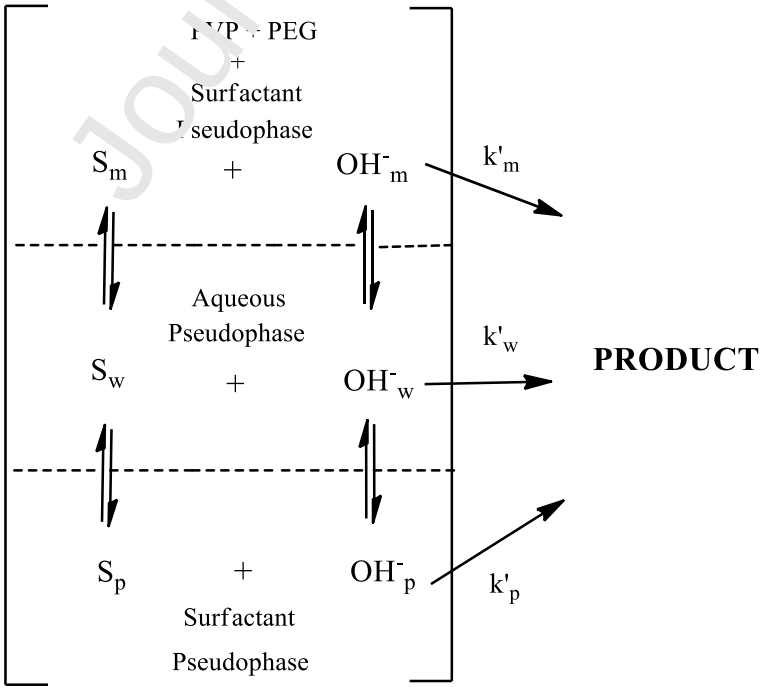
Scheme 1. Schematic representation of the interaction between PVP and PEG and its effect on benzocaine segregation



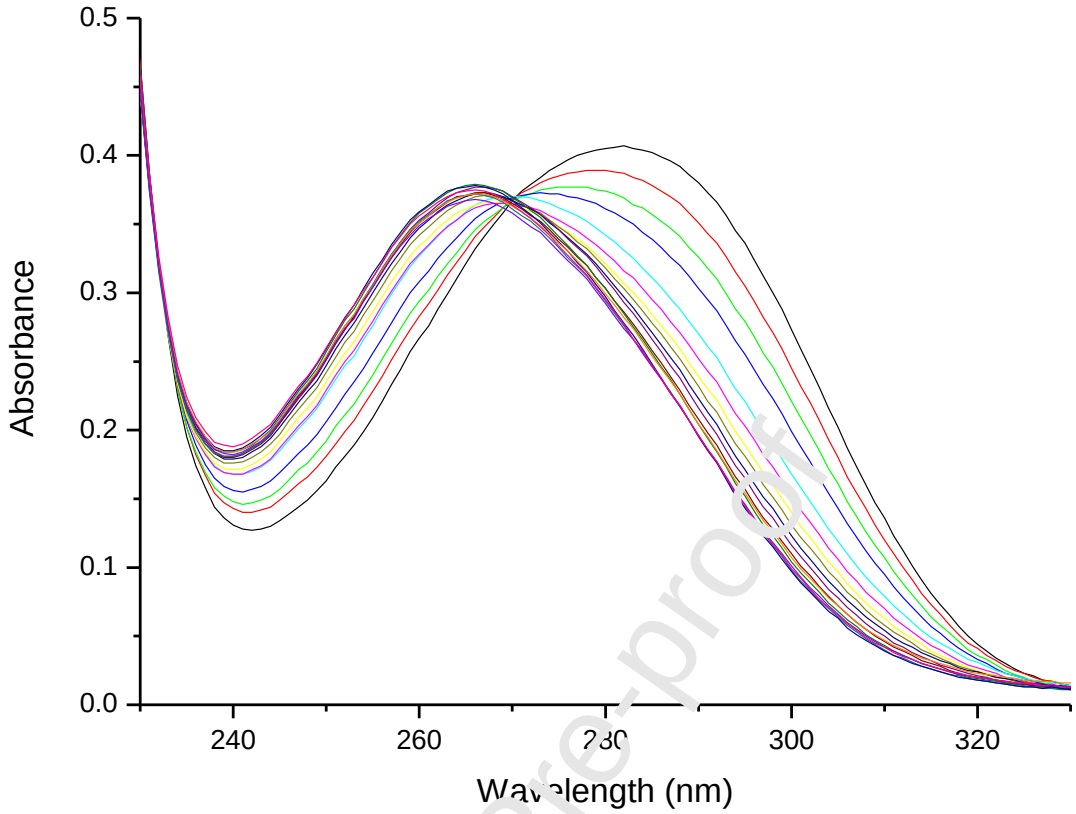
Scheme 2. Aggregated structure of a CTABr-PVP-PEG system in aqueous medium



Scheme 3. Aggregated structure of the SDS-PVP-PEG system in aqueous medium



Scheme 4. Distribution of the reactants in various pseudo-phases



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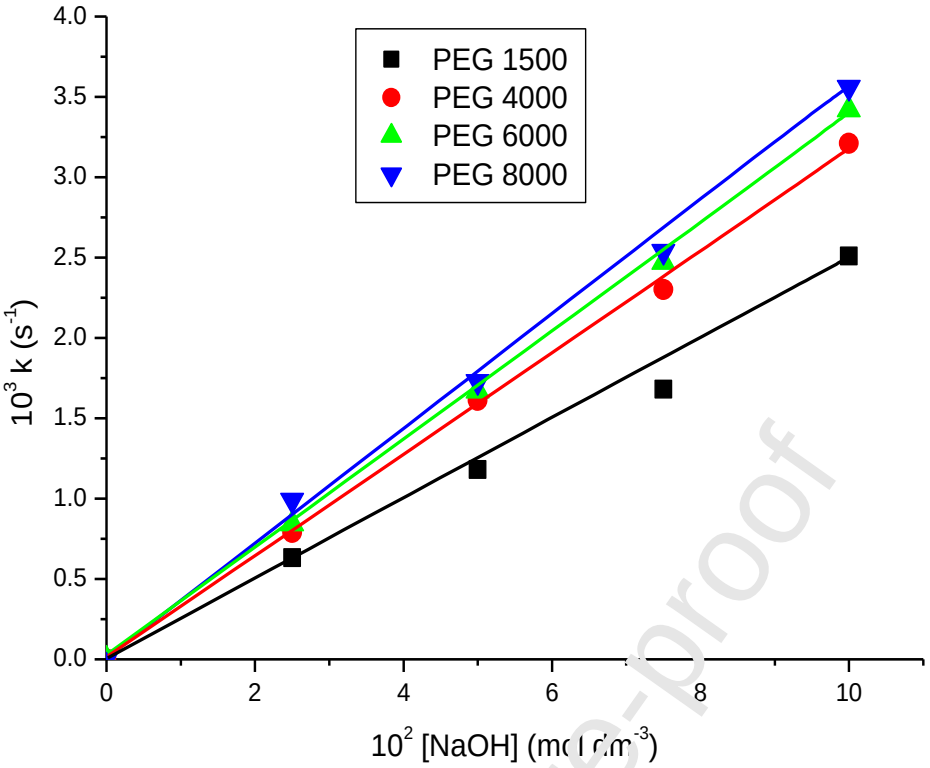

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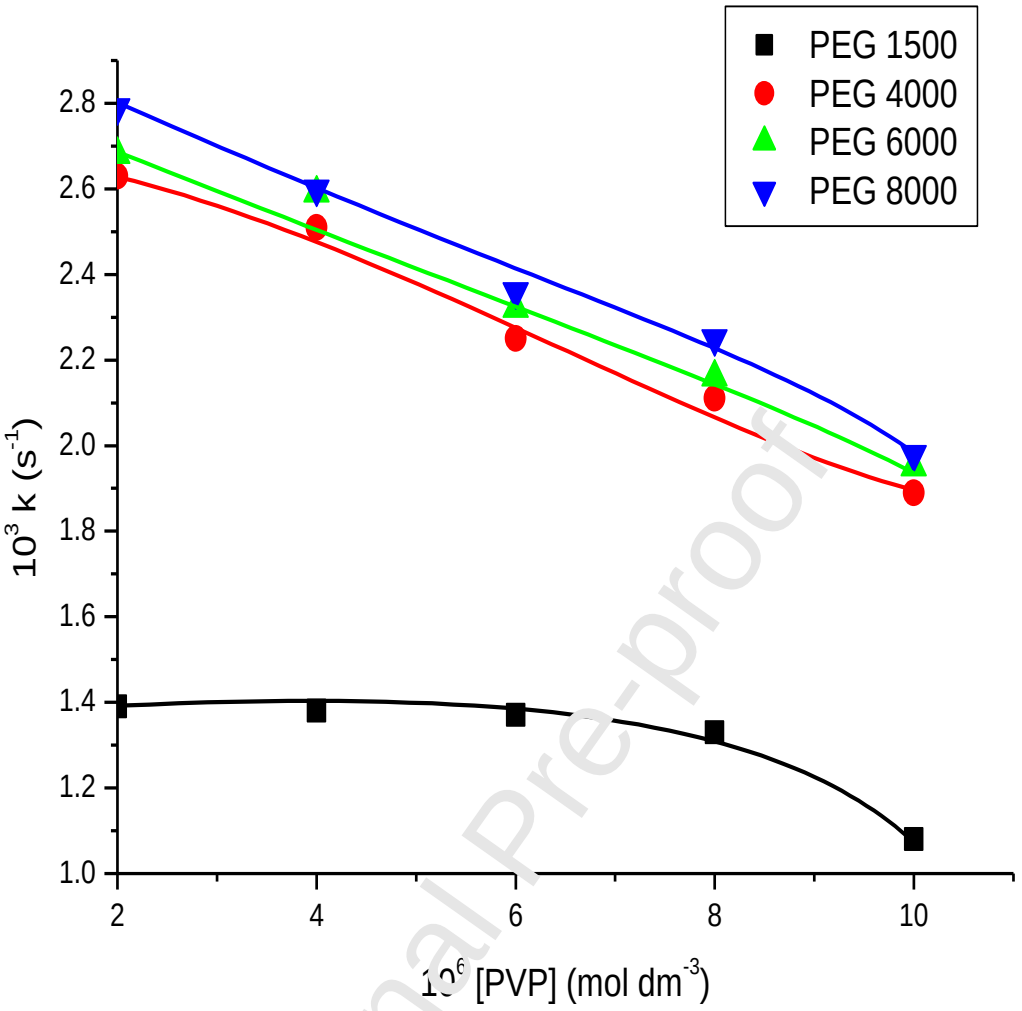
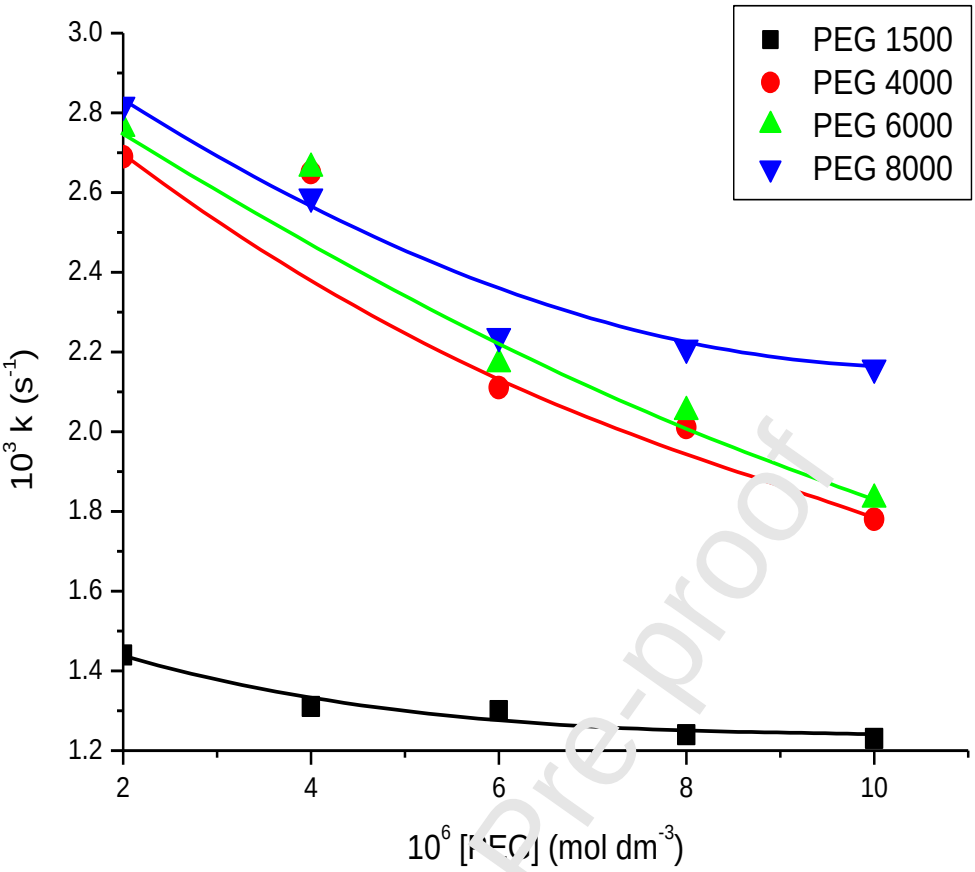


Fig. 3. Plot for the rate constant (k) *versus* [PVP] for the hydrolysis of benzocaine (3.0×10^{-5} mol dm^{-3}) in the presence of NaOH (5.0×10^{-2} mol dm^{-3}), PEG (6.0×10^{-6} mol dm^{-3}) and PVP (2.0×10^{-6} mol dm^{-3} to 10.0×10^{-6} mol dm^{-3}) at 40.0 ± 0.2°C.



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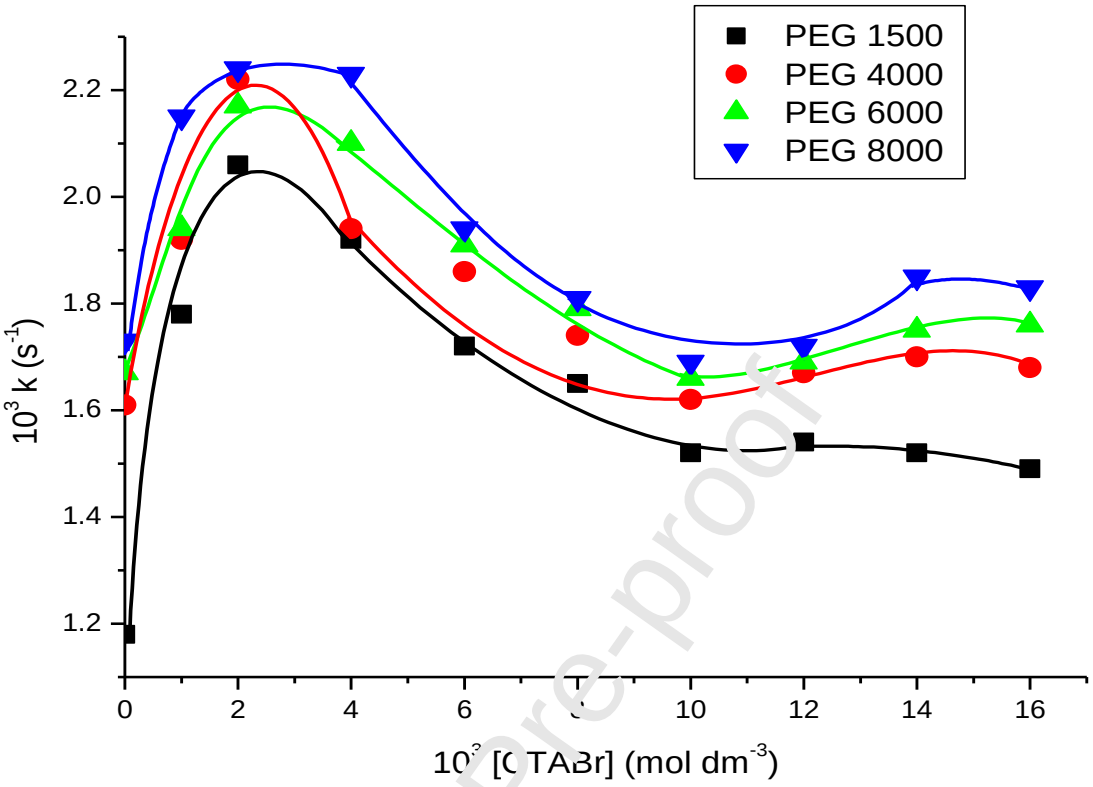

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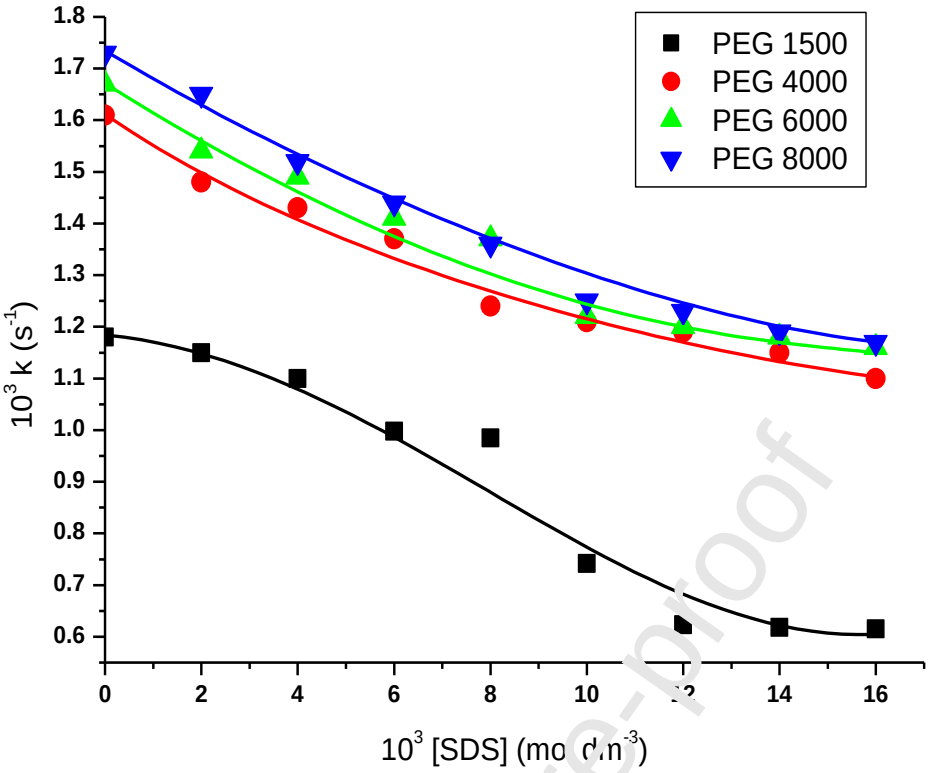

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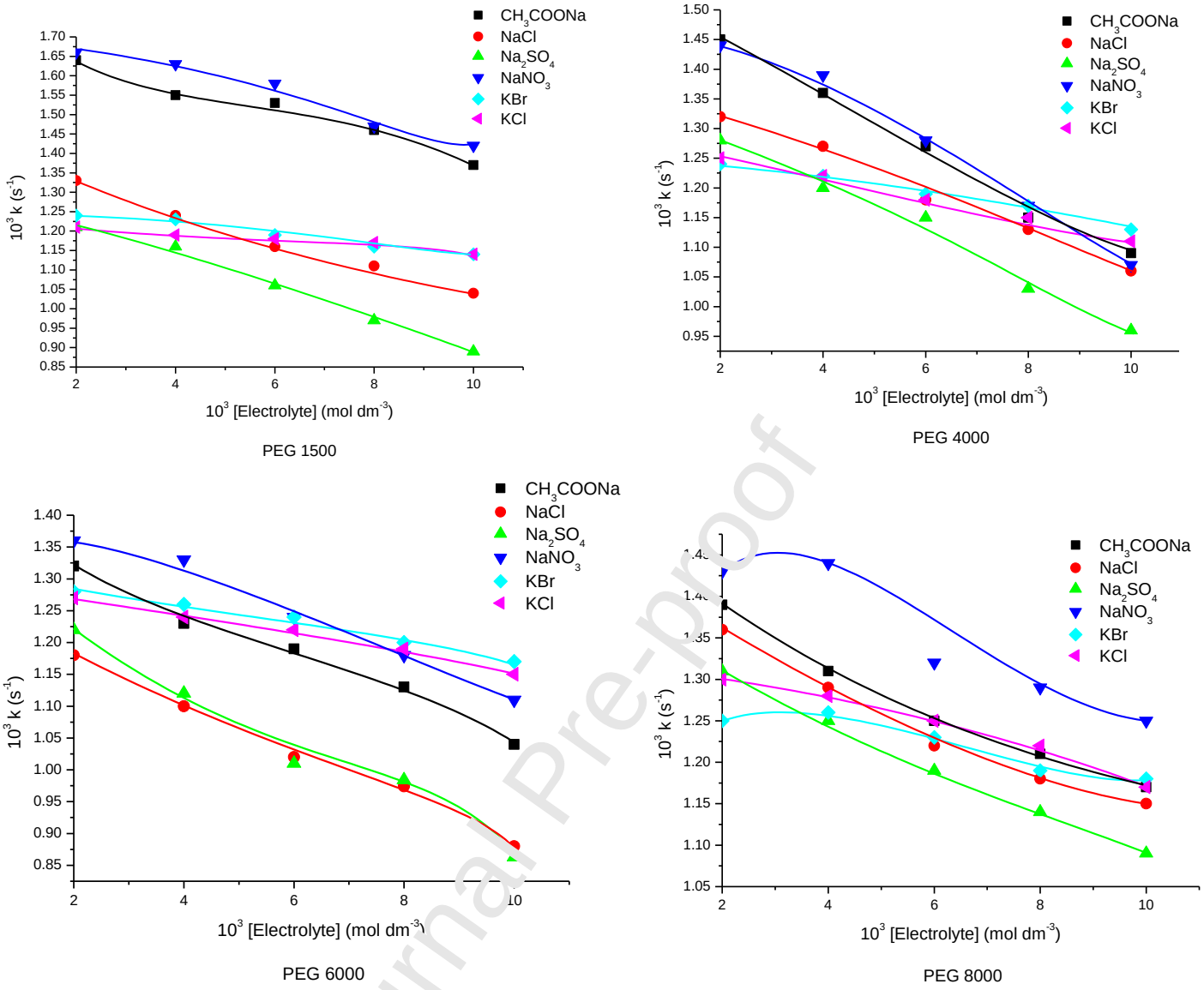

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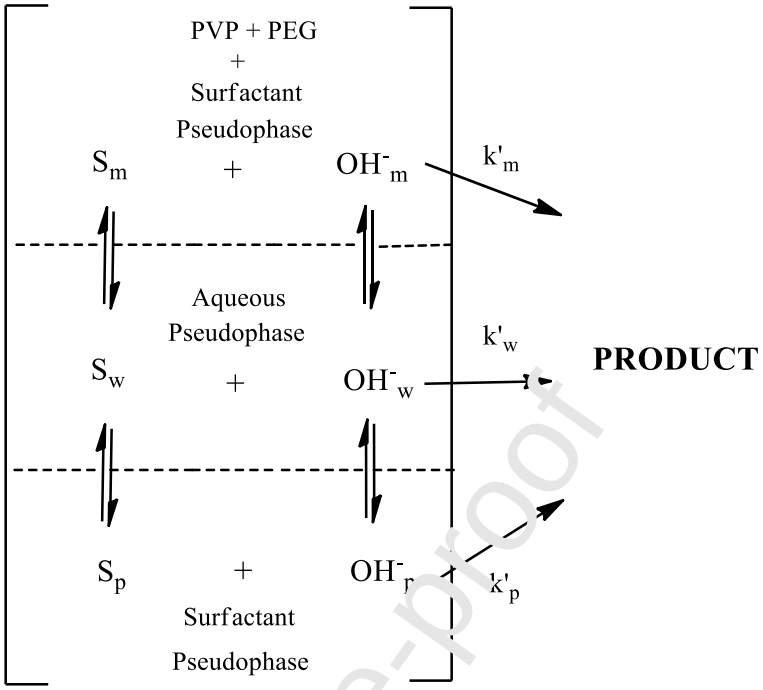
Graphical abstract



Research
Highlights

- The effect of the interaction between PVP and PEG, on the rate of alkaline hydrolysis of benzocaine was seen.
- The reaction rate decreased with the increase in [PVP] at fixed [PEG]; and also with the increase in [PEG] at fixed [PVP].
- The rate of hydrolysis of benzocaine in presence of CTABr has shown the peaked behavior.
- Electrolytes have found to decrease the rate of hydrolysis.