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HPMC effect on catalyzed hydrolysis of α-naphthyl acetate in cationic micellar systems

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Abstract

Micelle formation is an important property of surfactants. Micellar solutions of cetyltrimethylamonium bromide (CTAB) have been found to accelerate the hydrolysis of α-naphthyl acetate (α-NA) by *o*-iodosobenzoic acid (IBA), a strong nucleophile. Critical micelle concentration (CMC) of CTAB was determined in the absence and presence of various concentrations and grades of hydroxypropylmethyl cellulose (HPMC) using surface tension measurement. Reaction under pseudo-first-order condition was utilized for rate constant determination. The aggregation of CTAB in the polymer solution started at higher concentration than in the absence of the polymer. The observed rate constants for the degradation of α-NA in the presence of various concentrations of CTAB with and without HPMC were calculated. The presence of HPMC retarded the reaction rate. However, there was no obvious difference in the observed rate constant among the different grades of HPMC (Methocel E50®, Methocel E4M®, Methocel E10M®) while the higher the polymer concentration the lower the rate constant.

Keywords: Micelle; Kinetics; Polymer; Hydroxypropylmethylcellulose; Cetyltrimethylammonium bromide; Hydrolysis

1. Introduction

Surfactants have various applications in pharmaceutical area. The abilities to decrease surface tension and form micelles are important properties of surfactants. The critical micelle concentration (CMC) is a narrow range of surfactant concentration over which micelles first become detectable. A common technique to estimate CMC is determination of an inflection point from a linear-log plot of surface tension as a function of surfactant concentration.

The use of micellar solutions as reaction media has been an active area of research. Reaction kinetics may be altered in micellar solutions when compared to reactions in simple solutions (Berezin et al., 1973). The observed alteration is mainly due to the distribution of substrates between micellar and aqueous bulk phases, in which different environments exist (Fendler and Fendler, 1975). For example, the reaction between an anion and a neutral substrate is accelerated in a cationic micellar solution as shown in the hydrolysis of α-naphthyl acetate (α-NA) in the presence of *o*-iodosobenzoic acid (IBA) and cetyltrimethyl ammonium bromide (CTAB) micelles (Wurster and Patel, 1992). The hydrolysis of α-NA catalyzed by IBA follows first-order kinetic reaction with respect to α-NA concentration. The reaction involves a nucleophilic attack at the carbonyl carbon of α-NA by the reactive anionic form of IBA to form an acylated intermediate and α-naphthol anion (Scheme 1).

Interactions between polymers and surfactants have been found to alter of the solution-state properties of both (Allouche et al., 2003; Capalbi and La Mesa, 2001; Carlsson et al., 1989; Terayama et al., 2001). These interactions might cause reaction changes in micellar media. In this work, hydroxypropylmethylcellulose (HPMC, a non-ionic polymer) was introduced into CTAB micellar solutions. The influence of HPMC on CTAB micelle formation and on α-NA hydrolysis in the micellar solutions was investigated.

2. Materials and methods

2.1. Materials

Hydroxypropylmethyl cellulose (HPMC 2910) series: HPMC E50, HPMC E4M, and HPMC E10M (Methocel E50®,

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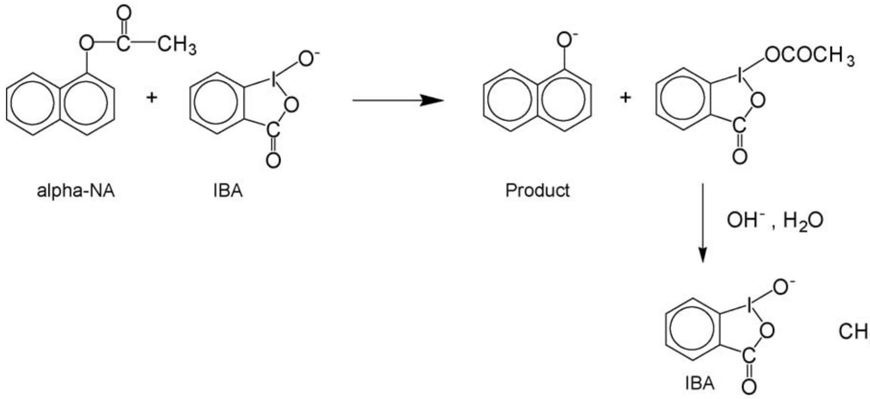

Scheme 1. A proposed reaction mechanism of α-NA hydrolysis in the presence of IBA, a catalyst.

Methocel E4M®, and Methocel E10M®) were obtained from The Dow Chemical Company, MI, USA. These HPMCs meet the specification that they contain 28–30% methoxyl substitution group and 7–12% hydroxypropoxyl substitution group (American Pharmaceuticl Association, 1986). Some of the material specifications of the used HPMC grades are presented in Table 1. Molecular weights and viscosities of the polymers were determined at 20 °C. Cetyltrimethyl ammonium bromide (CTAB), α-napthylacetate (α-NA) and *o*-iodosobenzoic acid (IBA) were purchased from Sigma Chemical Co., MO, USA. Monobasic sodium phosphate monohydrate, dibasic sodium phosphate, glacial acetic acid and sodium acetate were purchased from Merck KGaA, Darmstadt, Germany. The chemicals were used as received.

2.2. Critical micelle concentrations of CTAB and CTAB–HPMC mixed systems

2.2.1. Sample preparation

The CMC of CTAB ($\mathrm{CMC_{CTAB}}$) was determined in phosphate buffer. The total buffer concentration and pH were controlled at 0.0667 M and 7.4, respectively. HPMC (HPMC E50, HPMC E4M, and HPMC E10M) in the buffer solution were prepared to make 1 and 3%, by weight, polymer solutions. Various concentrations of CTAB from 1×10^{-6} to 8×10^{-3} M were prepared in the aforementioned solutions.

2.2.2. Surface tension measurement

A tension and interfacial tension torsion balance type ‘os’ (White Electrical Instrument Co., Ltd., Worcestershire, England) were employed in the studies. A platinum–iridium DuNoüy ring was attached to the instrument. The DuNoüy ring method measures the force required to detach a ring of fixed perimeter from the solution surface. The instruments were calibrated and all solutions were equilibrated in a water bath maintained at 30 °C before measuring the surface tension. The surface tension values were plotted against CTAB concentration on a logarithmic scale in order to calculate CMC for each system.

2.3. Hydrolysis kinetics of α-NA in micellar systems and the influence of HPMC

The effect of HPMCs on α-NA and IBA reaction in CTAB micellar solution was investigated in this study as a model reaction. The reaction was performed in phosphate buffer solution, pH 7.4 and 0.0667 M total buffer concentration, in the presence and the absence of polymers. Buffered solutions of 1%, by weight, HPMC (HPMC E50, HPMC E4M, and HPMC E10M) and 3%, by weight, HPMC E50 in the presence of CTAB (ranging in concentration from 0 to 6×10^{-3} M) were used as reaction media. The buffered solution of IBA was added and the mixture was very well mixed. α-NA in a small amount of alcohol USP was added to the mixture to initiate the reaction. Then, the mixture was vigorously mixed and incubated at 30 °C using a waterbath. pH values of the reaction media were measured using a pH meter at the beginning and at the end of the reaction. The initial concentrations of α-NA and IBA were 2.0×10^{-4} and 1.0×10^{-4} M, respectively. The reactions were performed in triplicate in each reaction medium. Samples were taken at appropriate times. Once a sample was taken, the reaction was immediately quenched by adjusting the sample pH to 4.5 using acetate buffer. The concentration of α-NA in the samples was analyzed using a spectrofluorometer-FP777 (Jasco Corporation, Japan). The excitation and emission wavelengths used for the analyses of α-NA were 277 and 334 nm, respectively. The hydrolysis

Table 1
General properties of Methocel® (HPMC)

Grade	Viscosity grade 2%, 20 °C (mPa s)	Number average molecular weight (Mn)	Number average degree of polymerization
HPMC E50	50	21234	114
HPMC E4M	4000	86000	460
HPMC E10M	10000	114486	608

The Dow Chemical Co. (2003).

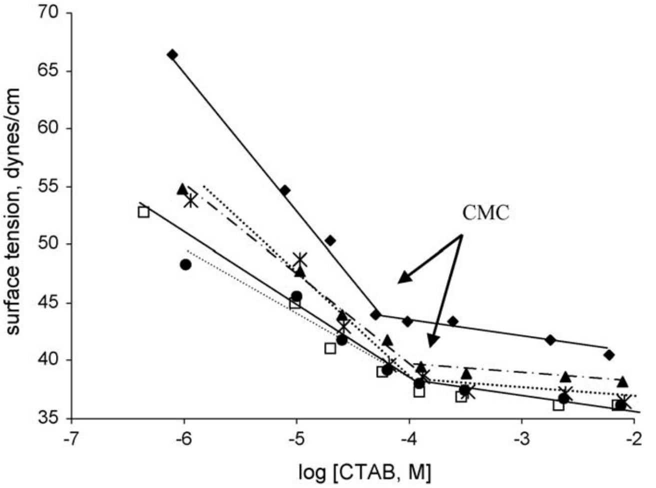

Fig. 1. Surface tension values of CTAB solutions at 30 °C in various media: (♦) without HPMC, (□) 1% HPMC E50, (●) 1% HPMC E4M, (▲) 1% HPMC E10M, (*) 3% HPMC E50 in phosphate buffer pH 7.4 employing a DuNoüy ring attached to a tensiometer.

rate constants were calculated from first-order plots. Observed rate constant versus CTAB micelle concentration profiles were constructed for each reaction medium.

3. Results

3.1. Critical micelle concentrations of CTAB and CTAB–HPMC mixed systems

Linear-log plots of surface tension versus CTAB concentration in different media are shown in Fig. 1. Surface tension rapidly drops as CTAB concentration increases up to a certain concentration. Then, surface tension gradually declines. The inflection point between the two slopes is defined as CMC. A summary of the $\mathrm{CMC}_{\mathrm{CTAB}}$ (critical micelle concentration of CTAB) in different media is reported in Table 2.

3.2. Hydrolysis kinetics of α-NA in micellar systems and the influence of HPMC

Typical first-order plots of α-NA hydrolysis in the presence of IBA are shown in Fig. 2. In the absence of CTAB micelles, the observed rate constants are $7.0 \times 10^{-4}\,\mathrm{min}^{-1}$ without HPMC, $7.1 \times 10^{-4}\,\mathrm{min}^{-1}$ in 1% HPMC E50, $7.6 \times 10^{-4}\,\mathrm{min}^{-1}$ in 1% HPMC E4M, $7.4 \times 10^{-4}\,\mathrm{min}^{-1}$ in 1% HPMC E10M, and $5.4 \times 10^{-4}\,\mathrm{min}^{-1}$ in 3% HPMC E50. The influence of HPMC and CTAB micelle concentration on the observed first-order rate constant is summarized in Fig. 3. The observed rate constant sharply increased as a function of micelle concentration and reached a maximum.

Table 2
CMC and surface excess of CTAB in phosphate buffer pH 7.4 at 30 °C ($n = 3$)

System	Mean CMC (M)	Surface excess (mol/cm^2)
Without HPMC	4.90×10^{-5}	10.49×10^{-11}
1% HPMC E50	1.15×10^{-4}	5.70×10^{-11}
1% HPMC E4M	1.14×10^{-4}	5.92×10^{-11}
1% HPMC E10M	1.40×10^{-4}	6.32×10^{-11}
3% HPMC E50	1.55×10^{-4}	6.78×10^{-11}

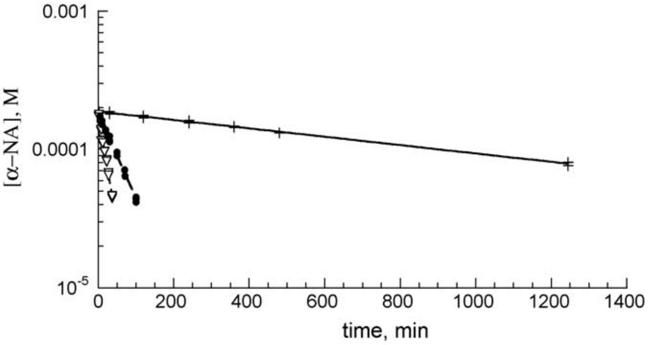

Fig. 2. First-order plot of α-NA hydrolysis in pH 7.4 phosphate buffer solution at 30 °C: (+) without CTAB and HPMC, (▽) 2.5 mM CTAB in the absence of HPMC, and (●) 2.5 mM CTAB in the presence of 1% HPMC E50.

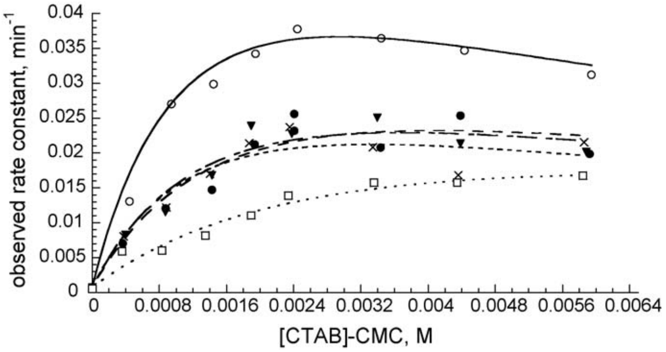

Fig. 3. The observed first-order rate constants of α-NA hydrolysis at various CTAB micelle concentrations in different media: (○) without HPMC, (▼) 1% HPMC E50, (●) 1% HPMC E4M, (×) 1% HPMC E10M, and (□) 3% HPMC E50.

4. Discussion

4.1. Critical micelle concentrations of CTAB and CTAB–HPMC mixed systems

In the absence of HPMC, the $\mathrm{CMC}_{\mathrm{CTAB}}$ in phosphate buffer was calculated to be 4.90×10^{-5} M at 30 °C. The $\mathrm{CMC}_{\mathrm{CTAB}}$ is previously reported with a value of 9.2×10^{-4} M at 25 °C in water (Fendler and Fendler, 1975). Generally, electrolytes decrease the repulsion between the similarly charged ionic head groups of the surfactant molecules; therefore, micellization is facilitated (Rosen, 2004). Thus, the $\mathrm{CMC}_{\mathrm{CTAB}}$ in buffer reported herein is less than the previously reported number in water.

The presence of HPMC increased $\mathrm{CMC}_{\mathrm{CTAB}}$ (Table 2). SPSS 14.0 for Windows evaluation (SPSS Inc., Illinois) was employed to analyze the experimental data. Fixed-effects one-way ANOVA analyses were performed to determine whether the means of $\mathrm{CMC}_{\mathrm{CTAB}}$ for each system were equal; i.e. H_0: $\mu_{\mathrm{CMC\ without\ HPMC}} = \mu_{\mathrm{CMC\ 1\%\ HPMC\ E50}} = \mu_{\mathrm{CMC\ 1\%\ HPMC\ E4M}} = \mu_{\mathrm{CMC\ 1\%\ HPMC\ E10M}} = \mu_{\mathrm{CMC\ 3\%\ HPMC\ E50}}$. From the F-table, $F_{3,10,0.95}$ is 3.48 which is less than the computed F-value of

7.303. The computed p-value of 0.005 is less than 0.05 (the α-value). Therefore, the means of $\mathrm{CMC_{CTAB}}$ are significantly different. The observed increase in $\mathrm{CMC_{CTAB}}$ in the presence of HPMC is also consistent with observations reported in other surfactant–polymer interaction studies. $\mathrm{CMC_{CTAB}}$ increased from 0.93 to 1.82 mM in CTAB-amylose system (Lundqvist et al., 2002). Furthermore, $\mathrm{CMC_{Tween80}}$ increased from 0.01 to 0.02% (w/w) to 0.5% (w/w) in the presence of 0.25% (w/w) Carbopol (Barreiro-Iglesias et al., 2003).

Tukey's test was used to determine which specific differences exist among the means using pair-wise comparisons. In the absence of HPMC, the mean of the $\mathrm{CMC_{CTAB}}$ is significantly lower than the mean of the $\mathrm{CMC_{CTAB}}$ in the presence of HPMC with computed p-values less than 0.020 ($\alpha = 0.05$). In the presence of 1% HPMC E50; 1% HPMC E4M; 1% HPMC E10M and 3% HPMC E50, the means of $\mathrm{CMC_{CTAB}}$ are not significantly different from each other with computed p-values greater than 0.924 ($\alpha = 0.05$). Interestingly, neither HPMC concentration (1 or 3% HPMC E50) nor HPMC molecular weight (1% HPMC E50, HPMC E4M, or HPMC E10M) have any significant effect on the $\mathrm{CMC_{CTAB}}$.

In the presence of HPMC, the increase in $\mathrm{CMC_{CTAB}}$ indicates that there is interaction between CTAB and HPMC. Therefore, more CTAB molecules are needed to reach the CMC. Another way to describe the effect of HPMC on $\mathrm{CMC_{CTAB}}$ is through the use of the Gibbs adsorption equation Eq. (1). The Gibbs adsorption equation describes mathematical relationship between surface tension and surfactant concentration as follows (Adamson and Gast, 1997):

$$\frac{d\gamma}{d\ln c} = -2RT\Gamma_1 \qquad (1)$$

where γ is the surface tension of the mixtures (dynes/cm), c the surfactant concentration (mol/L), R the gas constant (8.31×10^{-7} ergs $\mathrm{mol^{-1}\,K^{-1}}$), T the temperature (303.15 K in this work) and Γ_1 is the surface excess (mol/cm^2). The surface excesses of CTAB in each medium were calculated using Eq. (1) and are reported in Table 2. The decrease in surface excess of CTAB (almost by half) in the presence of HPMC suggests that there are less CTAB molecules at the liquid–air interface. HPMC has been reported to possess surface active properties (American Pharmaceuticl Association, 1986). Therefore, HPMC occupies some area at the interface and causes the surface excess of CTAB to decrease. Although the surface excess of CTAB was decreased in the presence of HPMC, the $\mathrm{CMC_{CTAB}}$ increased. This is likely due to an interaction between CTAB and HPMC in the bulk phase leading to a decrease in the effective concentration of CTAB to form micelles.

4.2. *Hydrolysis kinetics of α-NA in micellar systems and the influence of HPMC*

The good correlation observed from the first-order plots (Fig. 2) suggests that α-NA hydrolysis follows first-order kinetics. The reaction rate is described by the following differential equation:

$$\frac{d[\alpha-\mathrm{NA}]}{dt} = -k[\alpha-\mathrm{NA}][\mathrm{IBA}]$$

$$\text{or}\quad \frac{d[\alpha-\mathrm{NA}]}{dt} = -k_{\mathrm{obs}}[\alpha-\mathrm{NA}]$$

where $k_{\mathrm{obs}} = k[\mathrm{IBA}]$.

IBA is considered as a true catalyst for this reaction since its concentration is constant through out the reaction (Scheme 1). The observed reaction rate constant (k_{obs}) is a function of the effective concentration of IBA available for the reaction.

The presence of 2.39 mM CTAB micelle enhanced the observed rate constant of α-NA hydrolysis 54-fold when compared to the same system without CTAB micelles ($7.00 \times 10^{-4}\ \mathrm{min^{-1}}$ without CTAB micelles to $3.78 \times 10^{-2}\ \mathrm{min^{-1}}$ with micelles). Two mechanisms were proposed to explain this catalytic effect; i.e. an increase in substrate activities, and/or an increase in effective concentration of reactants in the presence of micelles (Mittal, 1976). The later mechanism is likely to be true in this study.

The chemical structure of α-NA suggests that this compound has a significant non-polar moiety and a polar one. Therefore, α-NA is expected to be solubilized in the palisade layer of CTAB micelles (Fig. 4). IBA, the catalyst, is likely to be drawn to the surface of micelle by ionic interactions between the negative charge of IBA and the positive charge of CTAB. In other words, reactants appear to concentrate in the small volume of the palisade layer of CTAB micelles. This results in an increase in the effective concentration of reactants.

In the absence of HPMC and presence of 1% HPMC, the observed rate constant increases as the concentration of CTAB micelles increases until a maximum is reached, after which the observed rate constant starts to decrease (Fig. 3). As the concentration of CTAB micelles increases, a point is reached at which maximum accumulation of α-NA and IBA in the micelles is achieved. After this point, the addition of further CTAB micelles results in redistribution (dilution) of α-NA and IBA in more micelles. Thus, the observed rate constant decreases.

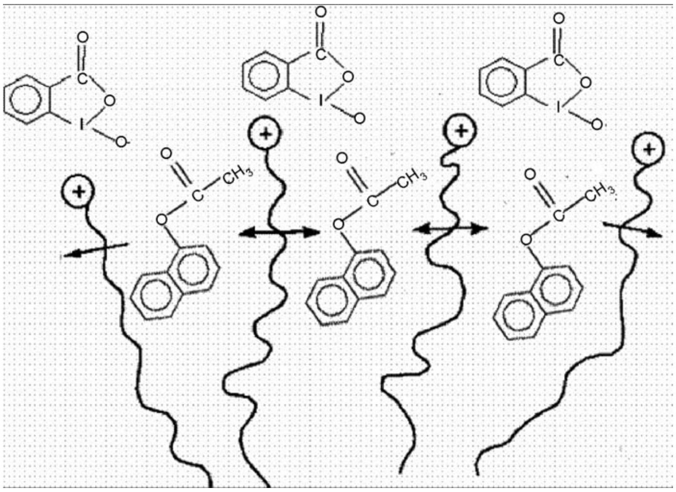

Fig. 4. Possible schematic representation for the orientation of α-NA and the dissociated form of IBA in/on the CTAB micelle.

To investigate the influence of a neutral polymer (HPMC) on the reaction rate constant, the reaction was performed in polymer solutions (Fig. 3). Without CTAB micelles, the mean observed rate constants in the absence of HPMC and the presence of 1% HPMC (irrespective of the grade) are not significantly different ($p > 0.05$; ANOVA analyses). One thing to emphasize is that solutions of different grades of HPMC (1%) have different viscosities. The aforementioned results indicate that the increase in the viscosity of the system upon the addition of 1% HPMC has no effect on the observed rate constant.

At, approximately, any given CTAB micelle concentration; the observed rate constants in the presence of HPMC are consistently lower than that in the absence of HPMC (Fig. 3). Therefore, in the presence of CTAB micelles, the decrease in the observed rate constant upon the addition of HPMC is likely due to an interaction between HPMC and CTAB micelles.

HPMC is composed of anhydroglucose monomer units. Therefore, an interaction between HPMC and CTAB micelles is likely to take place in the polar region of the micelle (close to the surface). Since the negatively charged IBA interacts with the positively charged micelle surface, an interaction between HPMC and CTAB micelles may hinder and decrease IBA concentration in the reaction region. The observed rate constant is a function of IBA concentration. Consequently, HPMC interaction with CTAB micelles results in a decrease in the observed rate constant.

All 1% HPMC solutions (irrespective of the grade) contain approximately the same concentration of anhydroglucose subunits. Therefore, the extent of CTAB–HPMC interaction is the same irrespective of HPMC grade. The observed rate constants in the different HPMC grade solutions (at a given CTAB concentration) are similar (Fig. 3) and underwent to the equivalent extent resulting in similar observed rate constants. The mean observed rate constant in the presence of 3% HPMC (at a given CTAB concentration) is significantly lower than the other mean observed rate constants with computed *p*-values less than 0.009 (Tukey HSD method). The 3% HPMC E50 solution contains more anhydroglucose subunits. Consequently, the extent of HPMC–CTAB interactions is greater and IBA effective concentration at the reaction region is smaller.

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