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ORIGINAL ARTICLE

Effect of reactive and non-reactive counterion micelles upon the alkaline degradation of indomethacin

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Abstract In the present paper, kinetics of alkaline degradation of well known drug, indomethacin (2-[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid), was studied in presence of excess [NaOH]. The rate of hydrolysis of substrate was independent of the [indomethacin] though it increased linearly with increasing the hydroxide ion concentration with a positive slope, suggesting the following rate law: $k_{obs} = k_1[OH^-]$. Cationic surfactants having non-reactive ions (cetyltrimethylammonium bromide, CTAB and cetyltrimethylammonium sulfate $(CTA)_2SO_4$) first increased the rate constants at lower concentrations and then decreased it at higher concentrations while in case of the surfactant with reactive counterions (cetyltrimethylammonium hydroxide, CTAOH) the rate increases sharply at lower concentrations of surfactant until it reaches to a plateau in contrast to the appearance of maxima in case of CTAB and $(CTA)_2SO_4$. Anionic surfactant, sodium dodecyl sulfate (SDS), inhibited the reaction rate at all concentrations used in the study. Pseudophase ion-exchange model was used for analyzing the effect of cationic micelles while the inhibition by SDS micelles was fitted using the Menger–Portnoy model. The effect of salts (NaCl, NaBr and $(CH_3)_4NBr$) was also seen on the hydrolysis of indomethacin and it was found that all salts inhibited the rate of reaction. The inhibition followed the trend NaCl < NaBr < $(CH_3)_4NBr$.

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1. Introduction

Various drug delivery and drug targeting systems have been developed in order to: (i) diminish drug degradation and loss, (ii) to avoid destructive side-effects, and to (iii) increase drug bioavailability and the amount of the drug accumulated in the vital zone. Among these systems, polymers, liposomes, nanoparticles, and surfactant are very common (Jain, 2008).

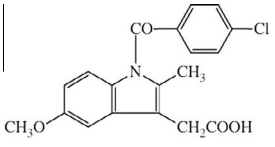
Surfactants form aggregated structures called micelles which contain hydrocarbon interiors and polar surfaces (Moroi, 1992; Rosen, 2004). Micelles provide different reactive

sites/microenvironments for different parts of reactant molecules (Khan, 2007). The hydrophobic nonpolar core is one of the probable sites that can gives binding energy to the hydrophobic parts of the reactants. The micellar surface can also interacts with the reactants' polar groups. Surfactants are capable to influence rate and equilibrium constants of numerous chemical processes (Al-Lohedan, 1990a,b, 1995; Kabir-ud-Din et al., 2007), because micelles are able to concentrate the reactants at the micelle–water interface called Stern layer (Savelli et al., 2001).

Since (i) the surfactants can enhance or retard the reaction rates and they are often used in the drug delivery formulations and (ii) the hydrolysis of drug is undesirable before it reaches to the site for completing its action; it is of particular interest to see the effect of surfactants micelles on the hydrolysis of drugs, especially, in alkaline medium. Surfactants micelles are useful in the protection of drugs from degradation as well as for solubilizing them in pharmaceutical formulations (Malmsten, 2002). Several investigators have studied the effect of micelles on the alkaline hydrolysis of various drugs (Broxton, 1982; Broxton et al.,1987, 1988; Cuenca, 2004; Ferrit et al., 2007, 2008). It is generally found that cationic surfactants with non-reactive counterions first increase and then decrease the rates of alkaline hydrolysis (maximum) while the surfactants with reactive counterions increase the rates (plateau). Anionic surfactants inhibit the rates of reactions. In our previous studies related to the drug hydrolysis, we have seen the effect of hydrophobicity of substrates as well as the effect of hydrophobicity of the surfactants and it was found in both studies that hydrophobicity plays an important role in the micelle–substrate interaction (Al-Ayed et al., 2011a; Al-Ayed et al., 2011b).

Indomethacin (2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-indol-3-yl]acetic acid) (Scheme 1), is a widely used non-steroidal anti-inflammatory agent with antipyretic and analgesic properties. Its anti-inflammatory activity relative to phenylbutazone varied from 10 to 85 times depending on the test employed (Shen et al., 1963). Antipyretic potency of indomethacin was approximately 10 times than aminopyrine. It is a light sensitive drug, stable in air, heat (under the usually prevailing condition), neutral, and slight acidic media. The side effects of indomethacin especially within the gastro-intestinal tract (ulceration, bleeding, etc.) occur when using peroral administration. In order to avoid these adverse effects, administration by injection has been considered. However, this compound is practically insoluble in water unless it is in alkaline media, where it undergoes hydrolysis. The alternative approach is to use the micelles, liposomes, cyclodextrin, etc.

Although the effect of surfactants on the alkaline hydrolysis have been attempted previously (Dawson et al., 1977; Krasowska, 1979, 1980; Cipiciani et al., 1985; Lin and Kawashima, 1985; Tomida et al., 1988), a comparison involving the effect of surfactants having reactive and non-reactive ions has not been done so far, therefore, in this paper we have studied a comparison between the catalysis by cationic surfactants having reactive and non-reactive counterions as well as anionic surfactant.



Scheme 1 Structure of Indomethacin.

2. Materials and methods

2.1. Materials

Indomethacin (97%, Sigma, USA), sodium dodecyl sulfate, SDS (99%, BDH, England), cetyltrimethylammonium bromide, CTAB (99%, Sigma, USA), sodium chloride (99.9%, Merck, Germany), and sodium bromide (99%, BDH, England) were used without further purification. Cetyltrimethylammonium hydroxide, CTAOH and cetyltrimethylammonium sulfate $(CTA)_2SO_4$ were synthesized and crystallized in the laboratory. Deionized double-distilled water (specific conductance: $1–2 \times 10^{-6}\ \Omega^{-1}\ cm^{-1}$) was used as a solvent.

2.2. Kinetic measurements

The kinetics of the reaction was followed by measuring the decay in the absorbance at 320 nm as a function of time with the help of a Perkin–Elmer 330 UV–visible spectrophotometer maintained at 25 ± 0.1 °C using L.K.B. 2209 multitemperature (Fig. 1). Critical micelle concentrations (cmc) under the reaction conditions were determined using Kruss Type 10 tensiometer. Rest of the kinetics experiment details are given elsewhere (Al-Ayed, 2002; Al-Ayed et al., 2011b).

3. Results and discussions

3.1. Alkaline hydrolysis of indomethacine in absence of surfactants

It is well known that the kinetics of aqueous hydrolysis of indomethacin is pH dependent. It includes three regions (i) below a pH of ≈3 which is specific acid catalysis region followed by (ii) a broad valley in the region of pH 3–5 and it is supposed to be the water attack region, and finally (iii) the linear region above pH 7 which indicates the specific base catalyzed region (Krasowska, 1979).

The kinetics of the alkaline hydrolysis of indomethacine have been studied (Dawson et al., 1977), by measuring the apparent first-order rate constants in the pH range of 11–12 at different temperatures. The involvement of mono-dissociated species of indomethacin with hydroxide ions was suggested in the reaction. Krasowska (1979) described a linear relationship between log rate constant versus pH (in the range of 7–10) at 50, 60 and 70 °C, implying that the aqueous degradation of the indomethacine is first-order overall. It is specific base catalyzed reaction and its degradation occurs primarily via hydrolysis of the amide moiety.

In our study, the rate of reaction of alkaline hydrolysis of indomethacin is independent of substrate concentration in the range of $1–15 \times 10^{-4}$ mol dm^{-4} indicating the first order dependence of the reaction on substrate (Table 1). Similarly the observed rate constant increases linearly with increase in the hydroxide ion concentration with zero intercept on the rate constant versus $[OH^-]$ plot (Fig. 2). This is also an indication of the first order dependence of hydroxide ion concentration.