

CATALYTIC BEHAVIOUR OF TWEENS (POLYSORBATES) THE DEGRADATION OF A LOCAL ANAESTHETIC DRUG

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ABSTRACT

The present study provides information about the catalytic behaviour of a micelle forming non-ionic surfactant on the hydrolysis of procaine in carbonate-bicarbonate buffer (pH 9.2). The effect of Tween 20, 40 and 60 between 0.2% - 2.0% and Tween 80 between 0.1% - 0.8% w/v on the reaction at 40°C - 70°C has been investigated. The non-ionic surfactant speeds up the rate of hydrolysis and exhibits a catalytic effect in the order: Tween 80 > Tween 60 > Tween 40 > Tween 20. The behaviour of Tweens 80 on the basis of "Surfactant effect ratio" (SER) has been explained at these temperatures.

INTRODUCTION

During the past decades, several attempts have been made to elucidate the mechanism that reveals the controlling factors in acceleration or retardation of various reactions at the micellar surface (Attwood and Florence 1983, Tadros 1984, Fadnavis *et al.*, 1985, Al-Lohenden 1987; Engberts *et al.*, 1987; Broxton *et al.*, 1988; Razvi and Beg 1990). Consequently, due to numerous parameters involved, recent studies focused the overall effect of a non-ionic surfactant on the rate of chemical reactions which is expected to be different than that of the ionic surfactants (Weckström and Rosenholm 1997; Ameri *et al.*, 1997; Das and Dogra 1998). The main differences between the two are: (i) poly (oxyethylene) moiety of the Tweens is highly substituted and (ii) the Tweens are the esters of fatty acids of different chain length. The structure of micelles of polyoxyethylene group is considered to be such that a hydrocarbon core considering predominantly, the hydrocarbon chains of surfactants molecules is surrounded by polyoxyethylene monostearate, the palisade layer. The regions of the sphere

presumably provide different natures of environment such as the water content, density and the electrical field to solubilize. Several studies have shown that the hydrophobicity and the aggregation number of structure of Tweens decreases with an increase in the Tween number (Drummond *et al.*, 1989; Bhattacharyya *et al.*, 1993, Shah *et al.*, 1994; Saha and Dogra 1994).

MATERIALS

All non-ionic surfactants (Tween 20, 40, 60, 80) were obtained from Merck and they were used without further purification. Procaine was also obtained from Merck (USP Grade) and was found to be chromatographically pure. It was dried at 60°C to a constant weight and was stored in a desiccator over Silica Gel. Water used throughout the work was double distilled through glass still.

METHODS

Volumetric flask for nonionic surfactant studies, all of 50 ml capacity, containing 40 ml of the appropriate buffer were placed at desired temperatures in a constant temperature water bath. The flasks were left

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in the bath until the buffer has equilibrated also equilibrated to required temperature (15-20 mins.). 10 ml of stock solution of procaine also equilibrated to required temperature was then pipetted into the reaction vessel (50 ml volumetric flask) giving total concentration of ester 0.01%. Stop watch was started and the

concentration of the drug as 0.001% which was maintained throughout the kinetic studies for UV absorbance reading.

Samples were withdrawn periodically and extent of reaction determined by recording the UV absorbance of these

Table I
Results of Replicate Experiments on the Hydrolysis of 0.001% Procaine at pH 9.20 (Carbonate – Bicarbonate Buffer) and 50°C in the Absence of Presence of 0.8% Tween 80 as obtained from Computerized least Square Regression Analysis

	In the Absence of Tween 80		Experiment III	In the presence of Tween 80	
	Experiment I	Experiment II		Experiment I	Experiment II
Rate Constant (min ⁻¹)	4.423 x 10 ⁻³	4.301 x 10 ⁻³	4.272 x 10 ⁻³	3.693 x 10 ⁻²	3.7551 x 10 ⁻²
Correlation Coefficient	0.9998	0.9990	0.9986	0.9993	0.9995
Standard Deviation of rate constant	1.9312 x 10 ⁻⁵	4.684 x 10 ⁻⁵	5.605 x 10 ⁻⁵	3.1578 x 10 ⁻⁴	3.1234 x 10 ⁻⁴
Intercept	1.9984	1.999	1.9980	1.9987	2.0010
(Percentage)	99.858	99.323	99.584	99.640	100.273
Standard Deviation of intercept	1.539 x 10 ⁻³	3.732 x 10 ⁻³	4.466 x 10 ⁻³	2.995 x 10 ⁻³	2.614 x 10 ⁻³
Ratio of the slope to its standard Deviation	229.80	918.00	762.17	103.21	120.22
Bartlett / t-test at 0.05 Probability level:					
Calculated	4.374			1.3075	
Tabulated	5.991			2.2622	

vessel was shaken vigorously and return to bath immediately. 5 ml of the sample was with-drawn and was transferred into another 50 ml flask which contain around 30 ml distilled water. The solution was shaken thoroughly and the volume was makeup by distilled water. This gave the total

samples at the maximum wave length of absorption of 290 nm. For hydrolytic studies, in the presence of surface active agents the volume of buffer in the reaction vessel was adjusted in such a way that after the addition of the appropriate amount of surfactant solution and 10 ml procaine solution the final

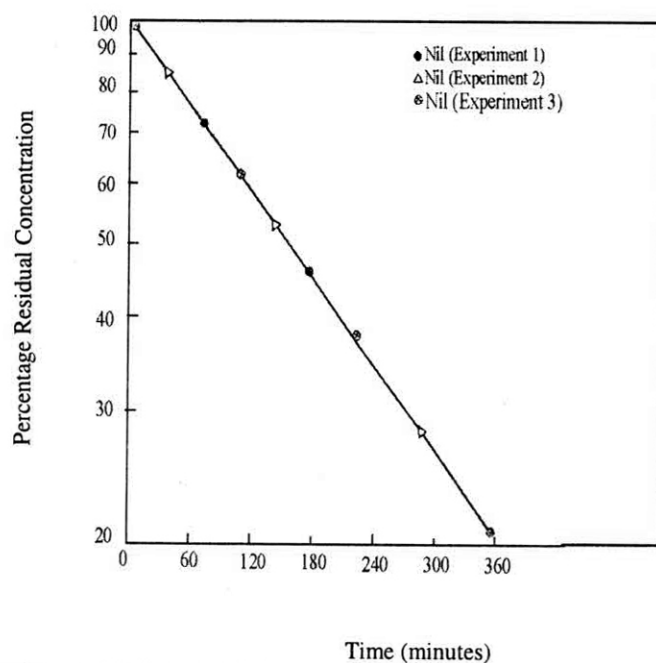


Fig. 1: Percentage residual concentration against time for the Hydrolysis of 0.001% procaine in carbonate – Bicarbonate buffer at pH 9.20 and 50°C in the absence of 0.8% Tween 80 for the replicate experiments. (For the sake of clarity only alternate points from (1), (2) and (3) are shown for non-surfactant system).

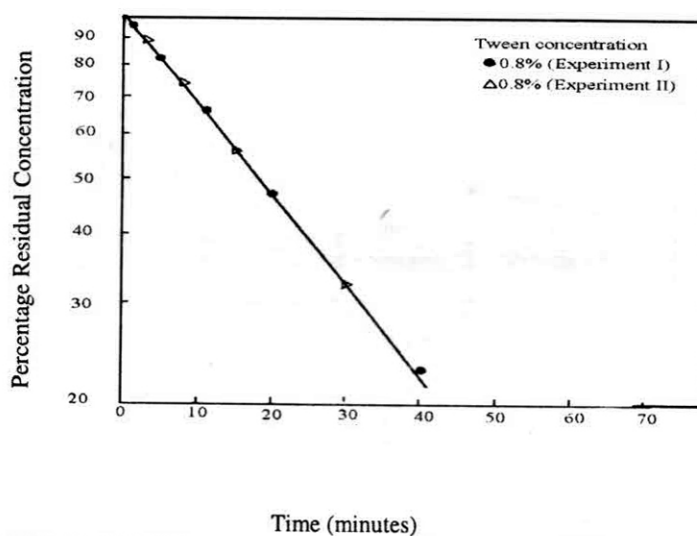


Fig. 2: Percentage residual concentration against time for the Hydrolysis of 0.001% procaine in carbonate – Bicarbonate buffer at pH 9.20 and 50°C in the absence of 0.8% Tween 80 for the replicate experiments. (For the sake of clarity only alternate points from (1) and (2) are shown for 0.8% Tween 80).

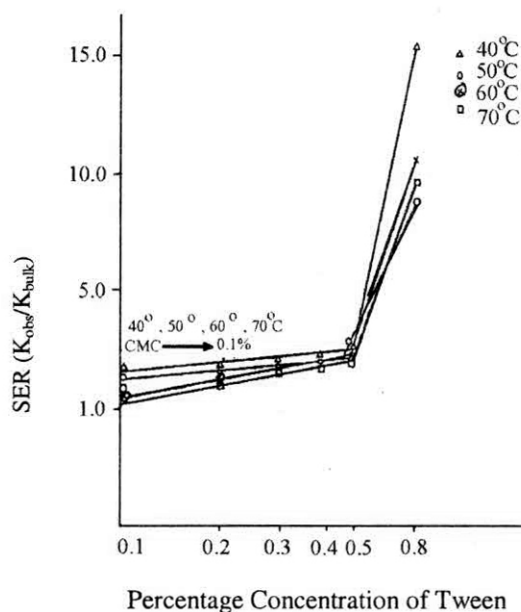


Fig. 3: The effect of Tween 80 on the Hydrolysis of 0.001% procaine at pH 9.20 at various temperatures in presence of carbonate – bicarbonate buffer expressed as ratio (K_{obs} / K_{bulk} of the first order rate constant obtained in the presence (K_{obs}) and absence (K_{bulk}) of surfactant.

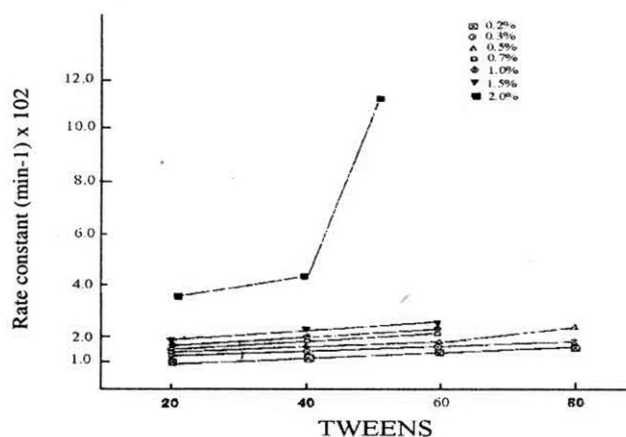


Fig. 4: A plot of rate constant against various concentration of Tweens at 60°C.

Determination of reproducibility of experimental technique:

Replicate experiments in the absence of Tween 80 and one set in the presence of Tween 80, the highest concentration used in the study (0.8%) were carried out. Percentage residual concentrations of the ester were

plotted against time according to first order kinetics (Figure 1 and 2). The data obtained for these replicate experiments were then subjected to statistical analysis and the rate constant (from the slopes) correlation coefficient, the intercept, standard deviation of the rate constants were calculated. These

value together with calculated and tabulated X^2 and t-test at the 5% ($p = 0.05$) probability level are shown in Table 1. The high correlation coefficients and the ratio of the slope to its standard deviation ($> .50$) gave good straight line showing that hydrolysis was followed by first-order kinetics. The low value of X^2 and t-test calculated compared to those of tabulated indicate that the results obtained from these replicate experiments are reproducible and assumed to the indistinguishable at the stated level.

RESULTS AND DISCUSSION

Non-ionic surfactants generally decrease the rate of hydrolysis of solubilized materials but in this case procaine proved to be an interesting agent as it exhibited catalysis (enhancement) in the presence of all Tweens studied in this project. A typical set of result is shown in Table 1 and Fig. 1 and 2. The effect of Tweens on the base-catalyzed hydrolysis of procaine can be well visualized from the SER-Tweens profiles whereas SER denotes the "Surfactant effect ratio in the presence and absence of Tweens. The typical set for profiles for Tween 80 at various temperatures is shown in Fig. 3. The plot shows that the SER increases slowly with increase in Tween concentration at various temperatures upto 0.5% and then there is quick rise in SER values for 0.8% concentration. This is probably due to sudden change in the shape of the micelle since it is known that the number of micelles increase in the concentration of surfactants above the CMCs and also at higher concentrations, micelles change their shapes from spherical to rodlike cylindrical shape. It is usually observed that hydrolysis involving hydrogen and hydroxyl ions is stabilized or not affected in the presences of nonionic surfactant, so the observation here contradicts the expected results.

Our investigation (Fig. 4) further indicates that while going from Tween 20 to Tween 80 the rate of hydrolysis continuously increases and such enhancement can easily be compared with non-surfactant as well as ionic

surfactant systems (Razvi 1989) at lower concentration between 0.2% and 1.5% the increase in rate constant is slow but at 2.0% concentration all Tweens with the exception of Tween 80 (rate constant with Tween 80 and 20% concentration could not be calculated since the value of extinction coefficient of drug with the Tween became less, compared to the value of its degradation product which resulted in negative values of rate constant) have a marked effect on the rate of hydrolysis of procaine. This effect is highly prominent for Tween 60.

The catalysis of Tween suggests that the drug is not penetrating into the micelles of non-ionic surfactants, in which case stabilization of the substrate would have been observed. This is true because the hydrocarbon core of the micelles contains very little water; if any, thus protecting the substrates (in case penetrated into the core of micelles) from being hydrolyzed by the bulk media. It should be noted that the external environment of the micelles formed from all Tweens differ from that of an anionic and cationic micelles, containing a poly-oxyethylene chain which is highly hydrophilic. The oxygen linkage in these non-ionic surfactants may interact with the drug and result in the increased rate of hydrolysis of the substrate.

Nonionic surface active agents have a number of properties which would be expected to give difference from the Equilibria found with many ionic materials. Unlike most surface-active agents they become less soluble at elevated temperatures, which is usually referred to as the clouding phenomenon, and they also have much lower melting points, frequently of being liquid at room temperature. Nonionic ethers have less tendency to form liquid crystal than ionic surface-active agents. These major differences in characters between nonionic and ionic surfactants account for the higher rate of hydrolysis of drug in presence of Tweens as compared to that of ionic surfactants.

The other that should be taken into account for the enhancement in the rate by these nonionic surfactants is high level of hydration of polyoxyethylene group which is believed to be due to the arrangement of the polyoxyethylene chains in the micelle (Elworthy *et al.*, 1960). This structure provides space for trapping of water molecules in the mesh of the polyoxyethylene chains, as well as hydration by hydrogen-bond formation between water molecules and ether oxygen of polyoxyethylene chains.

Examination of the existing literature suggests that for some nonionic micellar system, including several zwitterionic ones (Herrmann 1962 and Mukerjee 1972), the size distributions are quite narrow as compared to ionic micelles. Therefore, under such conditions there is a possibility that nonionic micelles could take up small amount of the substrate inside the micelle as compared to ionic surfactants. The rate of hydrolysis will thus be increased compared to that in the presence of ionic surfactants. Thus, procaine was initially localized in the semipolar, hydrate, region of polyoxyethylene chain and therefore may not be stable.

However, unexpectedly, enhancement in the rate of hydrolysis by Tweens compared to the system in the absence of surfactant as reported in this work is not fully understood. The enhancement in the rate by these nonionic surfactants could perhaps be due to their different action on the small aggregates of procaine since aggregation of procaine in aqueous solution with very low aggregation numbers are known (Farhadrich *et al.*, 1967, Johnson & Lubhum 1969 and Mukerjee 1972). At present it is unclear, what effect, if any, this phenomenon may have on the stability / degradation of aqueous solution of procaine.

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