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AN INVESTIGATION INTO THE EFFECT OF TEMPERATURE (ACTIVATION PARAMETERS) AND ALKYL CHAIN LENGTH OF MICELLER SYSTEMS ON THE STABILITY OF A LOCAL ANESTHETIC DRUG

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ABSTRACT: The study is concerned with the temperature (activation parameters) effect on the Hydrolysis of procaine in a micelle system. The work was carried out in the presence of carbonate bicarbonate buffer at pH 9.2 at 40°C-70"C. Kinetic studies revealed that the energy of activation above critical micelle concentration (erne) gradually increase with an increase in alkyl chain length of ionic surface active agents and gradually decreased with nonionic surface active agent. This was expected since the higher the energy of activation the greater the degree of stability. The study also provided information that allow with an increase in concentration of surface-active agents, an increase in enthalpy and entropy parameters occurs. This would suggested that a strong interaction between the drug molecule and the surface-active agent.

KEYWORDS: Hydrolysis, Alkyl chain length, energy of activation, enthalpy; entropy, stability.

INTRODUCTION

The development of pharmaceutical product requires a product spectrum expertise to lead it through the complex pathway from discovery through characterization of quality, efficiacy, and safety of a drug product. However, the stability of these products are extend to which it retain within specified limits, through out its period of storage and use in a modem formulation. Stability is an essential quality attributed for drug products (Laider, 1965, Lechman and Deluca 1976; Carstensen and Rhodes, 2000). Application of kinetics in pharmacy results in the production of more stable drug and to provide a sound basis for such studies that involve chemical reaction.

In rational design and evaluation of dosage forms for drug, the stability of the active component must be major criteria in determining their stability. The intensive of such approaches is considered be significant, as various publications bear witness during the last several decades. (Sina, *et ai.,* 1974; Kigasawa, *et ai.,* 1981; Liwanpo, *et ai1983;* Irwin; *et. ai,* 1984 and Gustawii and Ekstrand; 1986 Weckitrion and Rosenholm, 1997; Das and Dogra, 1998). Today, there are many pharmaceutical formulations where surfactants are used as adjuvant, such as emulsifier, wetting agents solubilizers and preservative (Fendler and Fendler, 1975; Oppenheim, 1976; Fusasaki and Murata, 1980; Bunton *et ai.,* 1982). Moreover several attempts have been made to elucidate the mechanism that reveals the controlling factors in acceleration or retardation of various reactions at the micelle surfaces (Attwood and Florence, 1983, Tadros 1984; Fadnavis, *et. ai* 1985; AI-Lohenden 1987; Engberts *et. ai,* 1987; Broxton *et. ai,* 1988; Razvi, 1989 Weckstrion and Rosenholm 1997).

Since the stabilization of procaine solution is carried out at higher temperature them at lower temperature (Higuchi, *et. ai1950)* there is a need of study various means of stabilizing procaine formulations, one of which could be the shielding of the procaine molecule from water via micellization. With this aim in view the present work initiated to assess the influences of temperature (activation parameters) effect and alky 1 chain length of ionic and non ionic surfactants in the hydrolysis of procaine in aqueous media at pH 9.20.

MATERIALS AND METHODS

Ester: This was procaine hydrochloride (v.S.P grade) obtained from Merck. A stock solution of 0.1 % procaine was made in distilled water for kinetics experiment and when not used it was kept in refrigerator. All reagents used in this study was A. R. Grade. The detail of the procedure is given elsewhere (Razvi, 1989).

Suifactant
Stock solution of 1xlO-IM cationic and anionic surfactants was prepared in carbonate-bicarbonate

buffer in previously aged volumetric flasks at 30°C. However, it was difficult to prepare the stock solution of Ixl0-JM for tetradecyl hexadecyl and octylsulphate at 30°C. Therefore, the stock solutions of these surfactants were prepared at 45° and 60°C respectively. The stock solution of sodium octyl sulphate was prepared at lxlO-3M because the compound was insoluble at higher concentration.

All non-ionic surfactants (Tween-20, 40, 60, 80) were obtained from mark and they were used without further purification. The were of different % prepared by w/v method and were used as such the effect of Tween-20, 40, 60, between 0.2 - 2.0 % and Tween-80 between 0.1 - 0.8% w/v on the reaction at 40-70°C

Water

It was freshly distilled from all glass-still using potassium permangnetic, which has a specific conductivity of < 10-0 ohm-Jcm-J and surface tension of 72.05 mNm-Jat 25°C.

Buffer

Carbonate-bicarbonate buffer at pH 9.20 was prepared according to (Bates, 1954). Few drops ofO.lN sodium hydroxide were used to maintain the appropriate pH of the buffer solution.

RESUL T AND DISCUSSION

The prediction of stability of a pharmaceutical compound may be made at ordinary, self-temperatures using the method of accelerated stability analysis, which is based on the temperature dependency of degradation reaction (the Arrhenius plot).

The Arrhenius plot for procaine in the absence and presence of all concentration of surfactants (anionic, cationic and nonionic) used during kinetic studies are shown in figures (1-12). The value of activation energy for the hydrolysis of procaine in the absence of surfactant j;, 17.6315 K. Cal. mole-J (Razvi, 1989), which comes in the usual range of activation energies for drags reported in literature (Higuchi *et al.*, 1950; Marcus and Baron, 1959 Kennon, 1964). The result also indicates that above the CMC regions as the concentrations of anionic and cationic surfactants increase, the activation energy for procaine also increases with the exception of nonionic surfactants where activation energies decreases with increasing their concentration. The values of activation energies increase with increasing the chain length of anionic and cationic surfactants. The non ionic surfactant system consistently shows a lower energy barrier, which is comparable with catalysis. Also supports the previous observation that the substrate is not on the suffer in a predominantly micelles environment all values of activation energy are in the agreement with those of the literature values for salvolytic processes e.g. reaction in solution which are in the range of 1030 K. Cal. mole (Lechman and Duluea, 1976). The anionic surfactants provide more degree of stabilization as it is reflected by the shelf life values comes out to be with sodium tetradecyl sulphate of concentration 6xlO-2m were the shelf-life for procaine at 25°C is shown as 57.92 days with the corresponding half-life of 382.2 days (Razvi, 1989)

To draw more conclusions from the Arrhenius plot, other activation parameter such as enthalpies and entropies of activation (~H and ~s respectively) were shown in figures (13-24). This would suggest that with increasing concentration of surfactants an increase in enthalpy and entropy changes takes place. Greater increase in enthalpy change for anionic surfactant compared to cationic surfactants would suggests that there is strong interaction between anionic surfactants and procaine molecules. Therefore the greater the interaction of surfactant with the drug, there would be more possibility for the reduction in the rate of hydrolysis. Addition of micelles of anionic surfactants, which leads to more increase in the activation enthalpy could be also due to unfavorable electrostatic interaction.

A further point underlying the highest degree of stabilization of the drug in presence of tetradecylsulphate could perhaps be understood from various entropy changes at different temperature as shown in figures (15 and 16). A more negative entropy change suggests that the molecules are activated prior to reaction and must undergo into a more orderly state. The micelles environment will be more ordered than a bulk hydrocarbon phase resulting in more decrease of entropy and greater increase in the number of micelles and therefore, more stabilization of the drug with increase in sodium tetradecylsuphate concentration. This would suggest that there is strong interaction between the drug molecule and the anionic surface-active at this concentration

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