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The influence of the structural characteristics of the substrate and the medium on the stability of triflusal and acetylsalicylic acid in micellar systems

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ABSTRACT

A spectrophotometric study of the alkaline hydrolysis of two salicylic acid (SA) derived drugs, performed on acetylsalicylic acid (ASA) and triflusal, both in the absence and presence of cationic micelles. In the absence of micelles, a catalytic effect is produced by the favoured OH^- ion in the molecule of triflusal, due to the presence of the trifluoromethyl group. The surfactants used were: hexadecyltrimethylammonium hydroxide (HDTAOH), hexadecyltrimethylammonium chloride (HDTACl), hexadecyltrimethylammonium bromide (HDTABr), hexadecylethyldimethylammonium bromide (HDEDABr) and tetradecyltrimethylammonium bromide (TDTABr). In micelles with reactive counterions, the pseudo-first-order rate constant (k_{obs}) increases with the increase in surfactant concentration, while in micelles with non-reactive counterions, the rate constant increased with surfactant concentration at low concentration, reaching a maximum, and decreased at high surfactant concentration, even to below the value found in the absence of micelle. The micellar binding constant of both drugs (K_S), the micellar rate constant (k_M) and the ion-exchange constant (K_X^{OH}) were determined according to variation in k_{obs} in relation to surfactant concentration, through the application of the pseudophase ion-exchange model (PPIE) proposed. The empirical parameters obtained were found to depend on the substrate and the surfactant structure, these parameters were: the counterion of the micelle, the size of the headgroup and the chain length of the hydrophobic tail of the surfactant.

1. Introduction

Salicylic acid (SA) or 2-hydroxybenzoic acid is the first chemically synthetic compoud used for therapeutic means as analgesic, anti-pyretic and antirheumatic drugs [1]. However, problems arising from gastric irritability have lead to the synthesis of better tolerated derivatives, constituting a family of drugs known as the salicylates. The most representative salicylate drug is ASA, which was first used for its pharmacological effects as an analgesic and antipyretic drug at the central nervous system level, and as an anti-inflammatory drug at peripheral nervous system level [2,3]. Subsequently, the continuous research carried out to discover more about the drug's action mechanism and to widen its possible therapeutic applications led to the discovery of its antiplatelet properties [4], and more recently, some authors even affirm its anticarcinogenic properties [5,6]. A more effective salicylate as an anti-inflamamtory, analgesic and antipyretic drug has been found. However, the successful use of triflusal as an antiplatelet drug is worthy of mention [4].

Both drugs have structural similarities given, that it is only two of the SA esters that are different in their chemical structure, due to the presence of a trifluoromethyl group in the C_4 of the aromatic ring, with regard to the acid group. The introduction of the fluorine atoms in the molecule gives rise to a modification in its chemical, physical and biological properties which are to be expected [4,7,8].

Currently, both drugs are widely used in therapy. However, the main problems associated with their use when administered orally are their secondary effects on the gastric mucosa, brought about by their acidic nature [4,9]. The pharmaceutical industry is therefore promoting the development of alternative forms of administration, but the main problems associated with the handling of these drugs is that they are of low solubility at acid pH and highly unstable at alkaline pH [10]. Numerous researchers have focused their attention on organised systems as alternative preparations, micelles [10–18], microemulsions [19–21] and liposomes [22]. Although micelles are not considered as a total or partial partition model with regard to biological membranes, they are structurally similar. Furthermore, they have the capacity to modify rates of chemical reaction, which have an important role in the formulation of pharmaceutical forms by reducing toxicity and increasing their stability. The alkaline hydrolysis of salicylates has been widely studied in micellar media, whose effects depend on substrate and surfactant structure. In the study of the substrate, the position and length of the chain of substituents have been taken into account. More concretely, the following substances have been studied: ASA [16–18,23], methylsalicylate [15,24], *n*-butyl salicylate [19], phenyl salicyalate [15,19,24–26], 5-octyl salicylate [10], 2-octyloxy benzoic acid [10] and 4-acetoxy benzoic acid [11]. With regard to surfactant structure,

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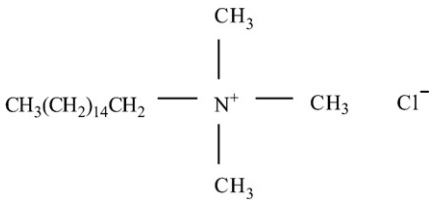
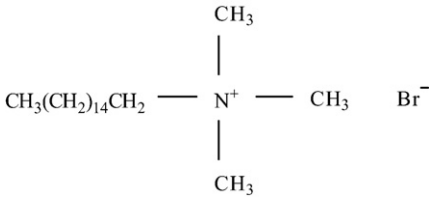
attention has been focused on its electrical charge. The cationic micelles HDTACl, HDTABr, HDEDMABr have an inhibitory effect on the alkaline hydrolysis of ASA [19,23,27], which is explained by the pseudophase ion-exchange model. However, the presence of sodium dodecyl sulfate micelles (SDS) increases the pseudo-first order rate constant with an increase in surfactant concentration, due to the formation of an ion-pair between the substrate and the cations of the micelles [18]. The rate of alkaline hydrolysis of ASA increases in W/O HDTAB/*n*-butanol/25% *n*-octanol/water microemulsions and decreases with the addition of water [28]. However, it is 55 times faster in reverse micelles of sodium-bis-(2-ethylhexyl)sulfosuccinate (AOT)/supercritical ethane [21] and 54 times faster in AOT/near-critical propane microemulsions [20]. The effects produced by other factors on such a reaction, such as temperature [12], acetronitrile and methanol concentrations were also studied [29].

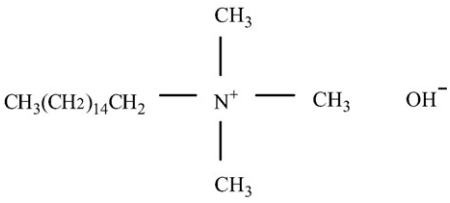
The purpose of the present work was to investigate the alkaline hydrolysis of ASA and triflusal in the presence and the absence of cationic micelles in an attempt to establish what influence the trifluoromethyl group exerts on this reaction. Prior to the micelle study stage, the physicochemical properties of the surfactant were determined through a conductimetric study. In the micellar system, an attempt was made to study the effects of both the substrate and surfactant structure. In order to do so, cationic surfactants, which varied in hydrocarbon chain length, size of surfactant headgroup and counterion of the micelle, were selected. The structures of the surfactants selected for this study are outlined below:



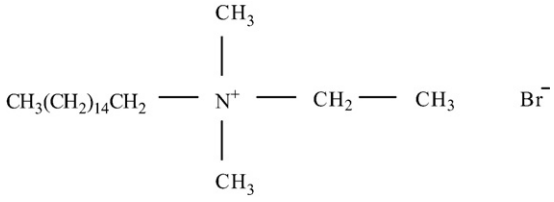
Hexadecyltrimethylammonium chloride (HDTACl)



Hexadecyltrimethylammonium bromide (HDTABr)



Hexadecyltrimethylammonium hydroxide (HDTAOH)



Hexadecylethyldimethylammonium bromide (HDEDMABr)

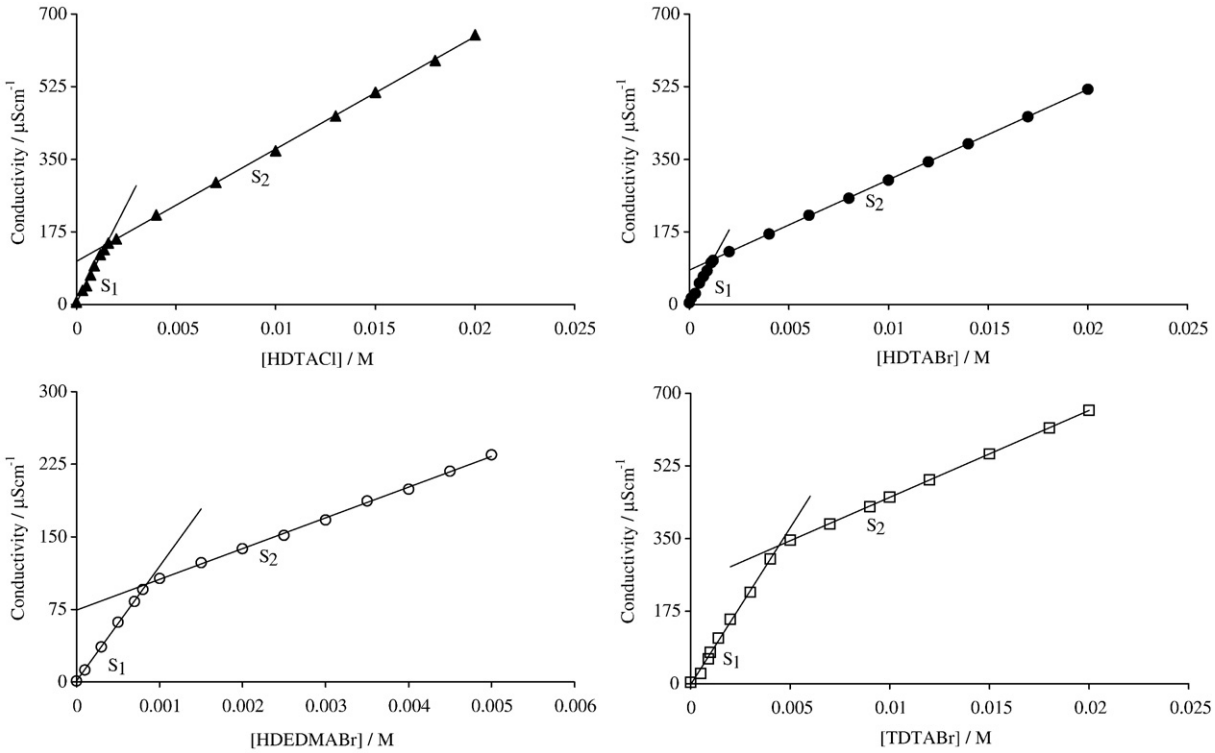


Fig. 1. Variation of conductivity versus surfactant concentration in micelles with non-reactive counterions. $T = 37 \pm 0.2$ °C.