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PARTITIONING OF QUINAPRIL ANION BETWEEN CETYLTRIMETHYLAMMONIUM BROMIDE MICELLES AND WATER

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Abstract

The interaction of the anion of quinapril (QUIN), angiotensin converting enzyme (ACE) inhibitor, with cationic surfactant cetyltrimethylammonium bromide (CTAB) was studied as a model system for drug/membrane interactions. From the dependence of differential absorbance at λ=272 nm on CTAB concentration, by using mathematical model that treats the solubilization of QUIN anion as its binding to specific sites in the micelles (Langmuir adsorption isotherm), the binding constant K_b was obtained.

Introduction

Drug interactions with heterogeneous media (micelles, lipid bilayer vesicles, biomembranes) induce changes in some physicochemical properties of the drugs (solubility, spectroscopic and acid-base properties) [1]. By monitoring these changes it is possible to quantify the degree of drug/micelle interaction which is expressed as micelle/water partition coefficient, K_x, and/or binding constant, K_b. Their elucidation is important for the understanding of interactions with biomembranes and for the quantitative structure-activity relationship of drugs, as well as for the use of surfactants in HPLC or MEKC in drug quality control.

In this work, the effect of cationic micelles of cetyltrimethylammonium bromide, CTAB, on the spectroscopic properties of the anion of angiotensin converting enzyme (ACE) inhibitor quinapril (3-isoquinolinecarboxylic acid, 2-[2-[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-monohydrochloride, $C_{25}H_{30}N_2O_5ClH$), QUIN is described. The absorption spectrophotometry was used to quantify the micelle/water partition coefficient and QUIN anion/micelle binding constant, by applying pseudo-phase [2] and Langmuir adsorption isotherm [3] mathematical models respectively.

Experimental

Spectrophotometric measurements were recorded on a Perkin-Elmer Lambda 35, double-beam UV-vis spectrophotometer with 1.0 cm quartz cuvettes at 25^0C. Instrumental conditions were: wavelength range 240 – 300 nm; slit width 1.0 nm; scan speed 60 nm min^{-1}. Stock solutions of 40 mM quinapril hydrochloride (Gödecke GmbH, Freiburg, Germany) were prepared by dissolving the compound in methanol.

Results and Discussion

Quinapril is a polyfunctional molecule with the pK_a values of 3.29 ± 0.40 and 5.38 ± 0.39 [4]. The absorption spectra of QUIN, both in aqueous and CTAB micellar solutions, were measured at pH=1.7 (QUIN cation) and pH=8 (QUIN anion). The effect of cationic micelles on the absorption spectrum of QUIN is observed only in basic solutions showing the importance of opposite charges in binding of quinapril ions to micelles. On adding CTAB the QUIN anion absorption maximum at 259.5 nm is shifted to 261 nm, with the formation of the shoulder at 264 nm and the pronounced new maximum at 272 nm (Figure 1). The batochromic shift observed is the consequence of the QUIN anion being transferred from the highly polar phase (water) to a less polar site (micelle surface layer).

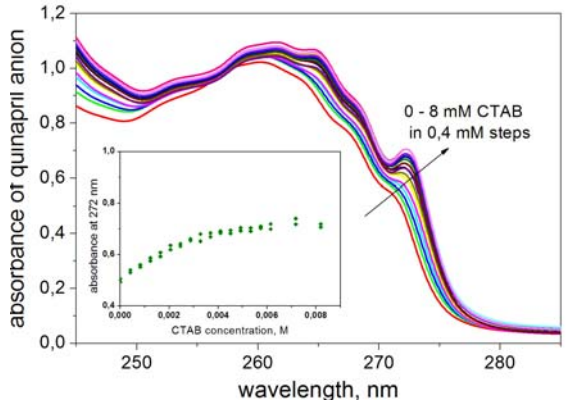

Fig. 1. Absorption spectra of 2mM QUIN containing increasing amounts of CTAB
Inset: A_{272} vs c_{CTAB}

The absorption spectra of 2 mM QUIN at pH=8 in the wavelength spectral range from 245 to 285 nm as a function of various concentrations of CTAB are depicted in Figure 1, with the inset showing the relation between A_{272} and c_{CTAB}. It is obvious that A_{272} asymptotically increases with increasing CTAB concentration, above its critical micelle concentration (CMC=0.5 mM determined by SLS), reaching the plateau (A_{272}^{∞}) when all added QUIN is solubilized in micelles. A_{272} can be used for the calculation of partition coefficient K_x, a thermodynamic parameter that represents the affinity of a given solubilizate to the micellar phase relative to the aqueous one, according to the pseudo-phase model [2]:

$$\frac{1}{\Delta A_{272}} = \frac{1}{\Delta A_{272}^{\infty}} + \frac{n_W}{K_X \cdot \Delta A_{272}^{\infty} \cdot (c_{QUIN} + c_{CTAB} - CMC)}$$

where $\Delta A_{272} = A_{272} - A_{272}^{w}$, $\Delta A_{272}^{\infty} = A_{272}^{\infty} - A_{272}^{w}$, A_{272}^{w} being the absorbance of QUIN anions in water and $n_w = 55.5$ M the molarity of water

The partition coefficients K_x evaluated for series of micellar solutions containing increasing concentrations of CTAB (c_{CTAB}= 0.5 – 8 mM) and solubilizing different

concentrations of quinapril (c_{QUIN}= 0.4 – 2 mM) were found to decrease with the increase of QUIN concentration. This indicates that solubilization is a competitive process that becomes progressively more difficult as the amount of drug incorporated into the micelles increases, the behavior being consistent with an adsorption-like phenomenon.

Hence, the solubilization of QUIN anion in CTAB micelles may be treated as an adsorption process by fitting the data to a Langmuir adsorption model [3]:

$$c_{QUIN}\,(1\text{-}f) = -\frac{1}{K_b} + \frac{c_{CTAB} - CMC}{n} * \frac{(1-f)}{f}$$

where $f = \Delta A_{272}/ \Delta A_{272}^{\infty}$ is the fraction of the associated QUIN anions, and n denotes the number of CTAB molecules forming the site for QUIN anion binding.

From the measurements of A_{272} in 2 mM QUIN containing increasing concentrations of CTAB (0.5 – 8 mM) at pH=8 following values of $K_b = (2.3 \pm 0.4) \times 10^3\ M^{-1}$ and $n = 0.94 \pm 0.09$ were obtained.

Conclusions

From the results obtained it was concluded that one CTAB molecule is forming the site for QUIN anion binding. QUIN anion is most probably situated in the micelle surface layer, with its aromatic part of the molecule immersed in the micelle and negatively charged carboxylate group at the same level as the positively charged quaternary ammonium groups of CTAB, both polar and electrostatic effects playing important role in its binding to CTAB micelles. The decrease of the partition coefficient with QUIN concentration is consistent with adsorption-like phenomenon.

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