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Note

Interaction of quinapril anion with cationic surfactant micelles of cetyltrimethylammonium bromide

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Abstract

In this study, the interaction of the anion of quinapril (QUIN), angiotensin converting enzyme (ACE) inhibitor, with cationic surfactant cetyltrimethylammonium bromide (CTAB) was investigated. The effect of cationic micelles on the spectroscopic and acid–base properties of QUIN was studied at pH 8. The binding of QUIN anion to CTAB micelles implied a shift in drug acidity constant ($pK_a^{water} - pK_a^{micelle} = 1.39$) proving the great affinity of negatively charged QUIN ion for the positively charged CTAB micelle surface. The strong dependence of the partition coefficient K_x on QUIN concentration, obtained by using pseudo-phase model, is consistent with an adsorption-like phenomenon. From the dependence of differential absorbance at $\lambda = 272$ 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 $K_b = (2.3 \pm 0.4) \times 10^3$ mol^{-1} dm^3 was obtained. QUIN–CTAB binding constant was also calculated from micellar liquid chromatography (MLC) and this method was found to be not accurate enough for its determination.

Keywords: Quinapril anion; CTAB; Micelles; Binding constant; Partition coefficient; MLC

1. Introduction

Micelles are aggregates formed by amphiphilic compounds (hydrophobic chain/hydrophilic head group) above their critical micelle concentration (CMC). The specific structure (hydrophilic surface/hydrophobic core) makes the micelles able to establish chemical interactions with either hydrophilic or lipophilic molecules [1,2].

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) [3,4]. By monitoring these changes it is possible to quantify the degree of drug/micelle interaction which is normally expressed as drug/micelle binding constant, K_b and micelle/water partition coefficient, K_x. The elucidation of these constants is important for the understanding of interactions with biomembranes, quantitative structure–activity relationship of drugs [5], micellar HPLC or micellar electrokinetic capillary chromatography (MEKC) used in drug quality control [6–11].

Quinapril (3-isoquinolinecarboxylic acid, 2-[2-[1-(ethoxycarbonyl)-3-phenylpropylamino]-1-oxopropyl]-1,2,3,4-tetrahydro-monohydrochloride, $C_{25}H_{30}N_2O_5ClH$, QUIN, Fig. 1) is a nonpeptide, nonsulfhydryl angiotensin converting enzyme (ACE) inhibitor belonging to the third class of ACE inhibitors. The role of this kind of drugs is to inhibit the last step of the biosynthesis of angiotensin II, a potent vasoconstrictor, causing general vasodilatation. Quinapril is used for the treatment of mild to moderate hypertension and congestive heart failure, either alone or in conjunction with other drugs [12–15].

2. Experimental

Experimental details are given in supplementary material.

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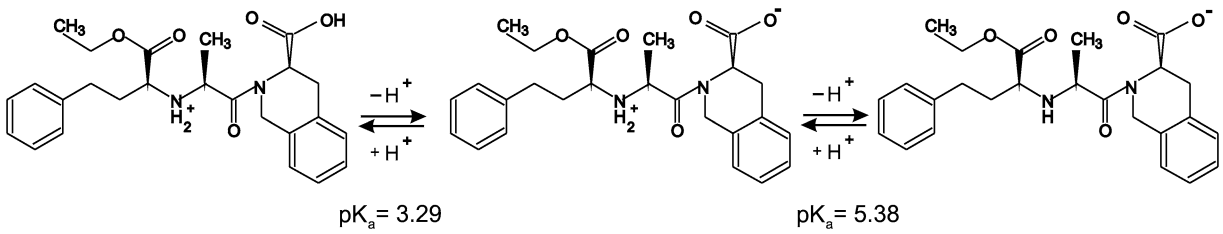

Fig. 1. Molecular structures of quinapril (QUIN).

3. Results and discussion

3.1. Absorption spectra and pK_a of QUIN in the presence of cationic micelles

Quinapril is a polyfunctional molecule with the pK_a values of 3.29 ± 0.40 and 5.38 ± 0.39 (Fig. 1, [9]). Therefore, at pH < 2 QUIN is a cation, while at pH > 7 it is an anion. The acidic aqueous solutions of QUIN recorded at pH = 1.7 in the wavelength range from 245 to 285 nm exhibit a characteristic absorption spectrum of cation with absorption maximum at $\lambda = 258$ nm. The absorption maximum of its anion obtained at pH = 8 experiences a slight batochromic shift ($\lambda = 259.5$ nm).

The addition of cationic surfactant cetyltrimethylammonium bromide (CTAB) has no influence on the QUIN cation spectrum. However, on adding CTAB in basic solution 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 (Fig. 2). The results obtained show the importance of opposite charges in binding of quinapril ions to micelles. Red shift is undoubtedly the consequence of the QUIN anion being transferred from the highly polar phase (water) to a less polar site [22]. From the inset of Fig. 2 it is obvious that A_{272} asymptotically increases with increasing CTAB concentration, above its critical micelle concentration, reaching the plateau when all added QUIN is solubilized in micelles. For increasing concentrations of QUIN the saturation is achieved at the increasing concentrations of CTAB. Unfortunately, the absorption method is not sensitive enough to obtain the value of CMC, hence it was determined by static light scattering measurements. In the solutions containing 5% v/v methanol, 2×10^{-3} mol dm^{-3} QUIN, pH = 8 the value of $\mathrm{CMC}_{\mathrm{CTAB}} = (5.0 \pm 0.5) \times 10^{-4}$ mol dm^{-3} was obtained (supporting material Fig. 1). This value is smaller than the CMC value reported in the literature ($\mathrm{CMC}_{\mathrm{CTAB}} = 9.2 \times 10^{-4}$ mol dm^{-3} [23]) which can be explained by the well-known lowering of the surfactant CMC upon influence of different compounds present [2], in this case OH^- and QUIN anions.

In order to solve the problem of a solubilized molecule position in the micelle it is useful to compare the spectra observed in the presence of the detergent with spectra in water/organic solvent mixtures of different polarities [2]. By recording the absorption spectra of QUIN in water/methanol and water/*tert*-butanol mixtures (Fig. 2 in supplementary material) characterized by different dielectric constants [16], and comparing them with the spectra in 8×10^{-3} mol dm^{-3} CTAB (Fig. 2), it may be concluded that the spectrum in CTAB micelles resembles those in the water/alcohol mixtures with dielectric constants lower than 40. However, it is obvious that the electrostatic interaction between positively charged micelle surface and QUIN anion negative charge has its role in micelle/drug binding. It is known that the octanol–water partition coefficient of QUIN anion is $\log D_{\mathrm{pH=8}} = 0.77$ (calculated using Advanced Chemistry Development Software Solaris V4.67 [17]), indicating its lipophilicity and affinity for the nonpolar phase. Since micelle surface is an environment differing in properties from water ($\varepsilon_{\mathrm{micelle\ surface}} = 36$ [18], 32 [19] and $\varepsilon_{\mathrm{water}} = 78.54$ [20]), QUIN anion is most probably situated in the micelle surface layer, both polar and electrostatic effects playing important role in its binding.

A shift in drug pK_a is the consequence of the preferential binding of one form of the drug, either the charged or the uncharged one, as well as the combination of electrostatic and microenvironmental effects of the micelles [2,3,19,21].

By measuring the increase of the absorbance at of 1×10^{-3} mol dm^{-3} QUIN in aqueous and micellar ($c_{\mathrm{CTAB}} = 5 \times 10^{-3}$ mol dm^{-3}) solutions on increasing the pH from 1.7 to 9, the acidity constants were estimated to be $\mathrm{p}K_{\mathrm{a}}^{\mathrm{water}} = 4.95 \pm 0.17$ and $\mathrm{p}K_{\mathrm{a}}^{\mathrm{micelle}} = 3.56 \pm 0.15$. The lowering of the p$K_a$ in micellar solutions ($\Delta \mathrm{p}K = 1.39$) proves the great affinity of QUIN anion for the positively charged CTAB micelle surface.

3.2. Determination of partition coefficient and binding constant

3.2.1. Determination by absorption spectrophotometry

In this work the absorption spectrophotometry was used to calculate partition coefficient, K_x, for QUIN anion between micellar and aqueous pseudo-phase and binding constant, K_b, of QUIN anion to CTAB. After comparing curves in Fig. 2 the most convenient absorption wavelength for the determination of K_x and K_b, was chosen to be $\lambda = 272$ nm. From the calibration curves of A_{272} versus c_{QUIN} in aqueous and micellar solutions ($c_{\mathrm{CTAB}} = 1 \times 10^{-2}$ mol dm^{-3}) for the concentration range of 1×10^{-4}–2.5×10^{-3} mol dm^{-3} absorptivities obtained are $\varepsilon_{272}^{\mathrm{w}} = 204 \pm 10$ mol^{-1} dm^3 cm^{-1} ($r = 0.999$) and $\varepsilon_{272}^{\mathrm{m}} = 372 \pm 15$ mol^{-1} dm^3 cm^{-1} ($r = 0.999$) for free and micelle-bound QUIN anion, respectively.

Since Lambert–Beer law holds for solubilized QUIN anions, 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 [24,25] K_x is determined from the following equation (elucidation given in

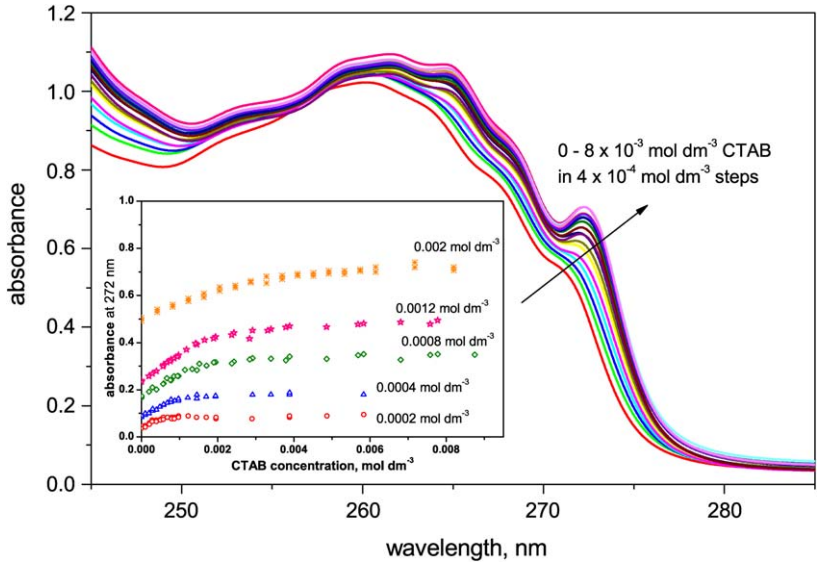

Fig. 2. Absorption spectra of 2×10^{-3} mol dm^{-3} QUIN at pH = 8 containing increasing amounts of CTAB. Inset: Absorbance at $\lambda = 272$ nm of various concentrations of QUIN as a function of CTAB concentration.

supplementary material)

$$\frac{1}{\Delta A_{272}} = \frac{1}{\Delta A_{272}^{\infty}} + \frac{n_{\mathrm{w}}}{K_x \Delta A_{272}^{\infty}(c_{\mathrm{QUIN}} + c_{\mathrm{CTAB}} - \mathrm{CMC})}, \quad (1)$$

where $\Delta A_{272} = A_{272} - A_{272}^{\mathrm{w}}$ and $\Delta A_{272}^{\infty} = A_{272}^{\infty} - A_{272}^{\mathrm{w}}$, A_{272}^{w} and A_{272}^{∞} being the absorbance of QUIN anions free and completely bound to CTAB, and $n_{\mathrm{w}} = 55.5$ mol dm^{-3} is the molarity of water. Hence, K_x is obtained from the slope of the plot of $1/\Delta A_{272}$ versus $1/(c_{\mathrm{QUIN}} + c_{\mathrm{CTAB}} - \mathrm{CMC})$ (Fig. 3 in supplementary material).

The partition coefficients were evaluated for series of micellar solutions containing increasing concentrations of CTAB ($c_{\mathrm{CTAB}} = 5 \times 10^{-4}$–$8 \times 10^{-3}$ mol dm^{-3}) and solubilizing different concentrations of quinapril ($c_{\mathrm{QUIN}} = 4 \times 10^{-4}$–$2 \times 10^{-3}$ mol dm^{-3}). The results summarized in Fig. 3 (Table 1 in supplementary material) show the partition coefficient being strongly dependent on the solubilizate concentration. The decrease of K_x with quinapril concentration indicates that solubilization is a competitive process that becomes progressively more difficult as the amount of drug incorporated into the micelles increases, behavior being consistent with an adsorption-like phenomenon.

Hence, the solubilization of quinapril anion in CTAB micelles may be treated as an adsorption process by fitting the data to a Langmuir adsorption isotherm model [26,27] (details given in supplementary material):

$$c_{\mathrm{QUIN}}(1-f) = -\frac{1}{K_{\mathrm{b}}} + \frac{c_{\mathrm{CTAB}} - \mathrm{CMC}}{n}\frac{(1-f)}{f}, \quad (2)$$

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. By plotting $c_{\mathrm{QUIN}}(1-f)$ versus $(c_{\mathrm{CTAB}} - \mathrm{CMC})(1-f)/f$ from the slope and intercept of the straight line the values of $1/n$ and $-1/K_{\mathrm{b}}$, respectively, should be obtained.

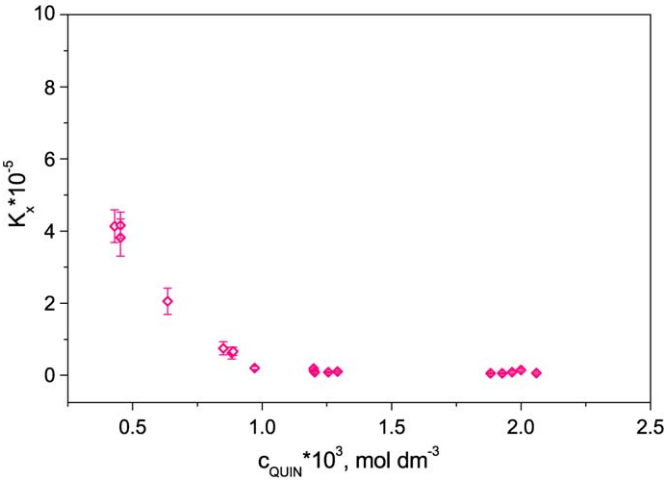

Fig. 3. Partition coefficient K_x as a function of QUIN anions concentration.

Since the wider range of crescent concentrations of CTAB until reaching plateau absorption of QUIN anions corresponds to higher QUIN concentrations, the binding constant was calculated from the results obtained in 2×10^{-3} mol dm^{-3} QUIN. The absorbance at $\lambda = 272$ nm was measured in five series ($n = 5$) of 2×10^{-3} mol dm^{-3} QUIN containing increasing concentrations of CTAB (5×10^{-4}–8×10^{-3} mol dm^{-3}). By using equation [2] and taking CMC to be 5×10^{-4} mol dm^{-3} the following values of $K_{\mathrm{b}} = (2.3 \pm 0.4) \times 10^3$ mol^{-1} dm^3 and $n = 0.94 \pm 0.09$ were obtained. Rather large uncertainty in K_{b} value arises from the small intercepts of the plots with substantial errors.

Since the n value corresponds to the average number of CTAB molecules surrounding each anion of QUIN, the value obtained confirms that one CTAB molecule is forming the site for QUIN anion binding. It is most probably located in the micelle with its aromatic ring immersed in the mi-

celle and negatively charged carboxylate group at the same level as the positively charged quaternary ammonium groups of CTAB.

3.2.2. Determination by MLC

Micellar liquid chromatography (MLC), where surfactants are present in the mobile phase in concentrations well above CMC, can be used for the determination of partition coefficients and/or binding constants [28,29]. According to Arunyanart and Cline Love [29] the dependence of the capacity factor of the solute, k', on the concentration of micellized surfactant $[M_m] = c_{surf} - CMC$ is defined with the following equation

$$\frac{1}{k'} = \frac{K_2[M_m]}{K_1\phi[L_s]} + \frac{1}{K_1\phi[L_s]}, \tag{3}$$

where ϕ is the phase ratio (the quotient between stationary and mobile phase volumes), K_2 solute–micelle binding constant, K_1 solute–stationary phase binding constant and $[L_s]$ the concentration of stationary phase sites. By plotting $1/k'$ versus $[M_m]$, the value of the solute/micelle binding constant K_2 per monomer of surfactant is obtained from the slope/intercept ratio.

The retention of QUIN anion on the polar stationary phase (alkyl nitrile saturated with CTAB) and methanol–0.02 mol dm^{-3} phosphate buffer (5:95 v/v) with 0.01 to 0.035 mol dm^{-3} CTAB added in 0.005 mol dm^{-3} increments, $pH^* = 7.4$ as mobile phase follows the behavior of class A compounds according to Jandera and Fischer [30]. The retention increases in submicellar mobile phases as the concentration of the surfactant is increased and decreases in micellar mobile phases as the concentration of micelles is raised.

By plotting $1/k'$ versus $[M_m]$ (Fig. 4 in supplementary material) the linear regression analysis gives $1/k' = (0.00506 \pm 0.00093) + (1.22552 \pm 0.03931) \times [M_m]$ and from the slope/intercept ratio the value of QUIN anion/CTAB binding constant $K_2 = (2.4 \pm 0.6) \times 10^2$ mol^{-1} dm^3 is obtained.

Binding constants obtained by using MLC and absorption spectrophotometry show great discrepancy of an order of magnitude. Since in MLC experiments, in order to achieve higher level of peak symmetry, phosphate buffer is added to mobile phase, we made additional determination of K_b in the presence of 0.02 mol dm^{-3} phosphate buffer by using absorption spectrophotometry. The value thus obtained $K_b = (1.6 \pm 0.2) \times 10^3$ mol^{-1} dm^3 is substantially lower then the value measured in the absence of buffer, $K_b = (2.3 \pm 0.4) \times 10^3$ mol^{-1} dm^3, the phenomenon expected according to the known salt effect on electrostatic interaction [31]. Unfortunately, the difference between K_b estimated by different methods is still too high. The main drawback of MLC method is the intrinsic error associated with the determination of K_2 from the slope/intercept ratio. Error propagation of a quotient affects the error in determining K_b, the error of the intercept being large when the intercept is very small, near to zero. Hence, we may conclude that in case of quinapril anion MLC is not the method of choice for the determination of its binding constant.

4. Concluding remarks

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 K_x with QUIN concentration is consistent with adsorption-like phenomenon. For the determination of binding constant from the Langmuir adsorption isotherm absorption spectrophotometry method was found to be more accurate then MLC.

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Supplementary material

The online version of this article contains additional supplementary material: Experimental details, determination of CMC by SLS, the effect of medium polarity on the absorption spectrum of QUIN, evaluation of the equations used for the determination of K_x and K_b, determination of partition coefficient K_x according to the pseudo-phase model, determination of K_b by MLC.

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