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STUDY OF VALSARTAN INTERACTION WITH MICELLES AS A MODEL SYSTEM FOR BIOMEMBRANE

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Abstract

The interaction of valsartan (VAL), an angiotensin II receptor antagonist, with cationic surfactant cetyltrimethylammonium bromide (CTAB) was investigated. To quantify the degree of VAL/CTAB interactions, two constants were calculated by using mathematical models: micelle/water partition coefficient and drug/micelle binding constant.

Introduction

Because of its amphiphilic nature, micelles are known to play a vital role in many processes of interest in both fundamental and applied sciences. The degree of drug/micelle interaction can be evaluated using two descriptors: micelle/water partition coefficient (K_x) and drug/micelle binding constant (K_b), by applying mathematical models [1]. The explanation of these constants is important for the understanding of interactions with biomembranes, QSAR (quantitative structure-activity relationship) studies, as well as the use of surfactants in HPLC in drug quality control. Micelle/water partition coefficient is known as an useful descriptor for hidrophobicity applied in QSAR studies and correlated with log *P* for a group of cephalosporins [2], barbiturates and steroids [3].

The aim of this work was to investigate the effect of cationic type of micelles on spectroscopic and acid-base properties of valsartan (N-(1-oxopentyl)-N-[[2'-(2H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine), using UV spectrophotometry at physiological conditions.

Experimental

Absorption spectra were recorded on a Cintra 20 spectrophotometer (GBC Scientific Pty. Ltd., Dandenong, Australia) equipped with 1.0 cm quartz cuvettes thermostated at 25°C and data processing Spectral 1.70 System Software. The optimized operating conditions were: wavelength range 225-335 nm; slit width 1.0 nm; scan speed 100 nm/min; data interval 0.960 nm. Stock solution of 10 mM valsartan (Novartis Pharma AG, Basel, Switzerland) was prepared by dissolving the compound in methanol.

Results and Discussion

Valsartan is a polyfunctional molecule with generally greater acidity of carboxylic group (pKa_1 = 3.9) and with pKa_2 = 4.9 attributed to the deprotonation of tetrazole group. The absorption spectra of VAL, both in aqueous and CTAB micellar solutions were measured at pH 2.8 (VAL molecule) and pH 7.4 (VAL dianion). Upon addition of CTAB into solutions at physiological pH, VAL dianion maximum at 250 nm shifted to 257 nm. A batochromic shift is undoubtedly the consequence of VAL dianion being transferred from highly polar phase (water) to a less polar site [4].

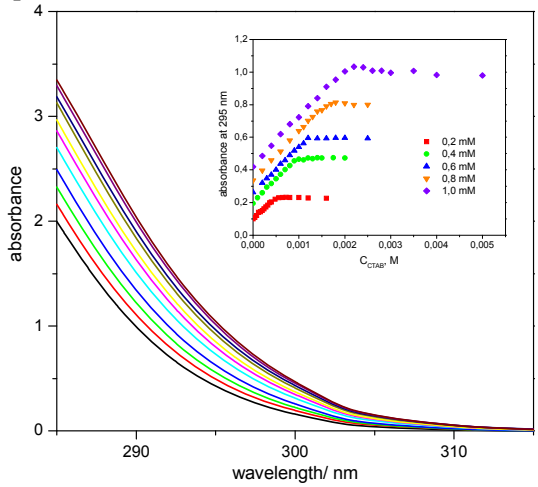

Fig. 1. Absorption spectra of 1 mM VAL containing increasing amounts of CTAB (C_{CTAB} = 0.2 – 5 mM). Inset: A_{295} vs C_{CTAB}

The absorption spectra of 1 mM VAL at pH 7.4 in the wavelength spectral range from 285 to 315 nm as a function of various concentrations of CTAB are depicted in Figure 1, with the inset showing the relation between A_{295} and C_{CTAB}. A_{295} asymptotically increases with increasing CTAB concentration, above its critical micelle concentration (CMC = 0.2 mM, determined by SLS), reaching the plateau when all added VAL is solubilized in micelles. A_{295} can be used for the calculation of K_x, according to the pseudo-phase model [5]. K_x represents the affinity of a given solubilizate to the micellar phase relative to the aqueous one and can be determined from the equation (1):

$$\frac{1}{\Delta A_{295}} = \frac{1}{\Delta A_{295}^{\infty}} + \frac{n_w}{K_x \cdot \Delta A_{295}^{\infty} \cdot (C_{VAL} + C_{CTAB} - CMC)} \qquad (1)$$

where $\Delta A_{295} = A_{295} - A_{295}^{water}$ and $\Delta A_{295}^{\infty} = A_{295}^{\infty} - A_{295}^{water}$, A_{295}^{water} and A_{295}^{∞} being the absorbance of VAL dianions free and completely bound to CTAB, respectively, and n_w = 55.5 M is the molarity of water.

The partition coefficients K_x were evaluated for series of micellar solutions containing increasing concentrations of CTAB (C_{CTAB} = 0.04-5 mM) and solubilizing different concentrations of VAL (C_{VAL} = 0.2-1 mM). The decrease of K_x with the increase of VAL concentration indicates that solubilization is a

competitive process that becomes progressively more difficult as the amount of drug incorporated into the micelles increases.

Hence, the solubilization of VAL dianion in CTAB micelles may be treated as an adsorption process by fitting the data to a Langmuir adsorption model [6]. The following expression (2) in linearized form is used:

$$C_{VAL} \cdot (1-f) = -\frac{1}{K_b} + \frac{C_{CTAB} - CMC}{n} \cdot \frac{(1-f)}{f} \qquad (2)$$

where $f = \Delta A_{295}/\Delta A_{295}^{\infty}$ is the fraction of the associated VAL dianions. From the measurements of A_{295} in 1 mM VAL containing increasing concentrations of CTAB (0.2-5 mM) at pH 7.4, following values of $K_b = (2.50 \pm 0.49)\cdot 10^4$ M^{-1} and $n = 1.24 \pm 0.13$ were obtained. The value of K_b correlates with the known higher lipophilic properties of VAL and provides support for strong hydrophobic interaction of VAL dianion with CTAB micelles. Since the n value corresponds to the average number of CTAB molecules surrounding each dianion of VAL, the value confirms that one CTAB molecule is forming the site for VAL dianion binding.

Conclusions

Valsartan dianion is most probably situated in the micelle surface layer, with biphenyl part of the molecule immersed in the micelle and negatively charged carboxilate located at the same level as the positively cherged quaternary ammonium groups of CTAB. In binding valsartan to CTAB micelles both polar and electrostatic effects play an important role. The decrease of K_x (calculated using pseudo-phase model) with VAL concentrations is consistent with adsorption-like phenomenon.

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