

Interaction of Losartan potassium with the micelles of Triton X 100

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ABSTRACT

This study is an investigation of the physicochemical interaction of Losartan potassium (LST K), an angiotensin-II receptor (type AT₁) antagonist, with micelles of triton X, a nonionic surfactant. The effect of micelles on the spectral properties of LSTK was monitored on at pH 7.4 and at room temperature. The spectrum of LST K showed gradual and progressive bathochromic and hypochromic shift in presence of increasing concentrations of triton X 100. The binding constant K_b of LST K to triton X 100 micelles was calculated using the differential absorbance at $\lambda = 225 \text{ nm}$ and was found to be $4.13 \pm 0.35 \times 10^5 \text{ mol}^{-1} \text{ L}$. By using pseudo-phase model, the partition coefficient between the bulk water and Triton X 100 micelles, K_x , was calculated from both differential absorbance ΔA_{225} , $K_x = 2.26 \pm 0.12 \times 10^5 \text{ mol}^{-1} \text{ L}$. The binding of LST K to Triton X 100 micelles implied a shift in drug acidity constant ($\Delta \text{p}K_a = 0.8$)

INTRODUCTION

LST K, 2-Butyl-4-chloro-1 [[2- (1H-tetrazol-5-yl)[1, 1_-biphenyl]-4-yl]methyl]-1Himidazole- 5-methanol, is a non-peptide angiotensin-II receptor (type AT₁) antagonist (Díez, 2006). It is an excellent antihypertensive drug, which is used in congestive heart failure (Lacourcière & Poirier, 2003). It is the prototype of a new class of antihypertensive agents, the angiotensin receptor antagonists and was approved in 1995 by the U.S.

Food and Drug Administration. Losartan has the potential to offer the advantage of increased selectivity, specificity and consistent blockade of circulating and tissue renin-angiotensin at AT₁ receptor level without some of the shortcomings associated with the use of ACE inhibitors (Zoumpoulakis *et al*, 2003; Johnson, 1995). Several methods have been described for the determination of LST K drug substance in tablets including high performance thin layer chromatography (McCarthy *et al*, 1998), radio receptor assay (Soldner *et al*, 1998), normal and reverse phase HPLC (Argekar & Sawant, 2000), Ritter *et al*, 1997, Bonfilio *et al*, 2009, Carlucci *et al*, 2000), capillary electrophoresis (CE) (Lastra *et al*, 2003) and spectrophotometric methods (Abd El-Hay *et al*, 2011; Hiemenz, 1986).

Micelles are formed from amphiphilic molecules, which possess hydrophobic chain as well as a hydrophilic head. Above a certain concentration, called critical micelle concentration (CMC), these molecules aggregate to form micelles. Due to their hydrophobic and hydrophilic regions, the micelles are able to establish chemical interactions with both hydrophilic and lipophilic drug molecules (Anitha *et al*, 2011). Micelles are known for their significance in biological, synthetic and energy-transfer systems wherein the solubilized species can under appropriate conditions serve either as an electron acceptor or as an electron donor. There are a variety of interactions, which may be operative between solubilized substrates and host micelles (Schreier *et al*, 2000).

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) (Castro *et al*, 2001; Tanaka *et al*, 1994). 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 (Ruiz *et al*, 2002), micellar HPLC or micellar electrokinetic capillary chromatography (MEKC) (Čudina *et al*, 2005; Duman *et al*, 2011).

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In this work, the effect of nonionic micelles of triton X 100 on the spectroscopic and acid–base properties of LST K is described. The absorption spectrophotometry were used to quantify the LST K/Triton X 100 binding constant and Triton X 100/water partition coefficient, by applying the mathematical models that consider partitioning of the drug between the micellar and aqueous pseudo-phases.

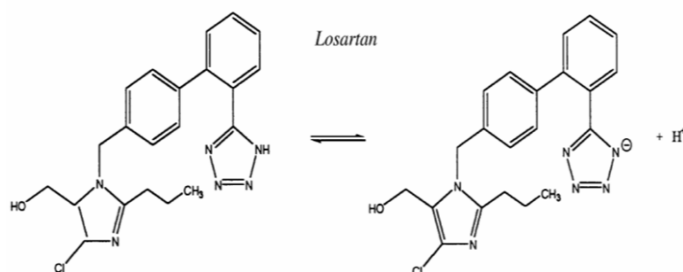


Fig. 1: Losartan Potassium.

EXPERIMENTAL

Instruments

Absorption spectra were recorded on Double beam Shimadzu (Japan) 1601 PC UV-VIS spectrophotometer connected to a computer fitted with UVPC personal spectroscopy software version 3.7, using matched quartz cuvettes in a thermostated cell holder. Measurements took place at 25 °C (± 0.2). The pH adjustments were carried out using Jenway pH-meter 3310 pH/ mV/ °C.

Materials

Reference Samples

Losartan potassium was kindly provided by Alkan Pharma, Egypt. Purity was reported to be $100.0 \pm 0.2\%$.

Reagents

All chemicals used were of analytical grade. Triton X 100 was purchased from Sigma, Germany. Disodium hydrogen phosphate and citric acid (anhydrous) were obtained from BDH Prolabo UK. Double-distilled water was used. All reagents were handled under fumehood.

Standard solutions

Stock solution of 4.34×10^{-4} M LST K was prepared by dissolving the drug in citrate-phosphate buffer pH 7.4. Stock solution of 0.002 M Triton X 100 was prepared by dissolving an appropriate amount of the surfactant in the same buffer. The final concentrations were prepared by diluting appropriate aliquots from stock solution using citrate-phosphate buffer pH 7.4.

Losartan- Triton X 100 interactions

Drug/micelle binding constant and micelle/water partition coefficient were determined by measuring absorption of fixed concentration of the drug (4.34×10^{-5} M) LST K and increasing concentrations of Triton X 100 (1×10^{-5} – 2.5×10^{-4})

against same concentration of Triton X 100 as blank at 225 nm. The effect of Triton X 100 on pK_a of LST K was studied using 4.34×10^{-5} M LST K in 0.01M Triton X 100. The spectrum of the acid solution was first obtained at a pH 1.8, where LST is present wholly as a molecular species. This spectrum was then compared with that of the purely ionized species similarly isolated at pH 7.4. The wavelength, where the greatest change in absorbance was observed, was chosen. At this wavelength and at various intermediate pH values, the absorbance values of the acid solutions were recorded. All absorbance measurements were corrected with the help of blank solutions containing the same concentration of surfactant in the buffer of required pH and were done at 25 ± 0.1 °C.

RESULTS AND DISCUSSION

UV spectrum of Losartan K

The UV spectrum of aqueous unbuffered solution of LST K shows a maximum close to 200 nm and a shoulder extending from 240 to 260 nm. At pH 7.4, peak absorbance was observed at 228 nm. In presence of Triton X 100, the absorption maximum at 228 nm suffered a slight shift to longer wavelength (red shift to 235 nm), accompanied by a hypochromic shift. The decrease in absorbance was monitored for $43.38 \mu\text{M}$ LST ($20 \mu\text{g ml}^{-1}$) in four series ($n=4$) containing increasing concentrations of Triton X 100 (1×10^{-5} – 2.5×10^{-4}) as shown in figure (2)

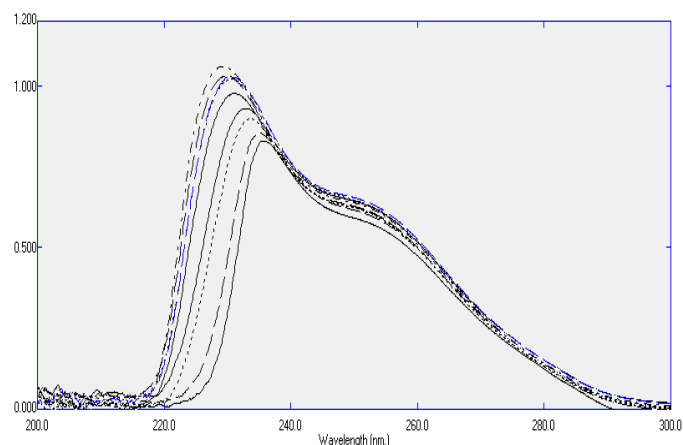


Fig. 2: The absorbance spectrum of $43.38 \mu\text{M}$ LST ($20 \mu\text{g ml}^{-1}$) in absence and in presence of increasing concentrations of Triton X 100 (1×10^{-5} – 2.5×10^{-4} M).

Losartan K- Triton X 100 interactions

Better understanding of drug/micelle interaction is not only achieved by explaining its nature, but also by quantifying its magnitude through the elucidation of drug/micelle binding constant and/or partition coefficient. Whenever the interactions of the molecule with its surrounding environment are intrinsically related to spectral characteristics, their changes can be used for the determination of corresponding binding constants and partition coefficients. The highest difference in absorbance of LST K alone and its absorbance in presence of Triton X 100 was observed at 225 nm, thus it was selected as the analytical wavelength for the study. The critical micelle concentration (CMC), the concentration

above which surfactant exists in micellar form, was calculated for Triton X 100. Although the absorption method is not the most sensitive method to obtain the value of CMC, CMC is the concentration of surfactant below which the absorbance at 225 nm should be the same in aqueous and non micellar surfactant solution, it is accepted to assume that, the CMC value of Triton X 100 is 1.66×10^{-5} M in presence of 43.38 μ M LST. This value is below the CMC reported in literature, and this can be explained by the well-known lowering of surfactant CMC under the influence of different additives and ions (Zaghbani *et al.*, 2011, Ćudina *et al.*, 2008). The increase in absorbance with the increase in surfactant concentration above CMC is regarded to be caused by the incorporation of drug molecules to micelles. As more drug molecules are incorporated to micelles the absorbance reaches a maximal value then becomes almost constant (Sepulveda *et al.*, 1986).

The degree of LST /surfactant interaction was quantified by calculating the LST /micelle binding constant (K_b) according to the following equations (Sepulveda *et al.*, 1986):

For the LST K in water, Lambert-Beer's law holds as experimentally confirmed.

$$A_{225}^w = \epsilon_{225}^w \times C_{LST} \quad [1]$$

Where A_{225}^w and ϵ_{225}^w represent the absorbance and the molar absorptivity at λ 225 nm and 1 cm optical path length. This equation also holds below CMC, in the nonmicellar surfactant solution.

In the micellar region, a portion of LST K, C_{LST}^m , is considered to be solubilized in micelles while the other portion, C_{LST}^w , still remains in the water region. The total concentration of LST is

$$C_{LST} = C_{LST}^m + C_{LST}^w \quad [2]$$

Assuming that Lambert-Beer's law also holds for the solubilized LST, the absorbance of micellar solution can be expressed as

$$A_{225} = \epsilon_{225}^m \times C_{LST}^m + \epsilon_{225}^w \times C_{LST}^w \quad [3]$$

Where, ϵ_{225}^m is the molar absorptivity for the solubilized LST.

The fraction f of the associated LST may be defined as

$$f = C_{LST}^m / C_{LST} \quad [4]$$

At a certain C_{LST} , f is equal to zero in the nonmicellar region up to CMC and increases with increasing the concentration of surfactant (C_{SAA}) above CMC. As C_{SAA} increases up to infinity, f approaches unity since all added LST should be solubilized in micelles, i.e. $C_{LST}^m \approx C_{LST}$.

Using equations [1], [2] and [3], the fraction f can be directly calculated from the experimental data by

$$f = \Delta A_{225} / \Delta A_{225}^\infty \quad [5]$$

Where $\Delta A_{225} = A_{225} - A_{225}^w$ and $\Delta A_{225}^\infty = A_{225}^\infty - A_{225}^w$,

A_{225} is the measured absorbance of LST in presence of a given concentration of surfactant, A_{225}^w is the absorbance of the same

concentration of LST in absence of surfactant and A_{225}^∞ being the absorbance of LST completely bound to surfactant.

The binding of LST to SAA micelles is at equilibrium,



With the equilibrium (binding) constant given by

$$K_b = C_{LST-SAA} / C_{LST}^w \cdot C_{SAA} \quad [6]$$

Where $C_{LST-SAA}$ is the concentration of micellar "sites" occupied by LST, C_{LST}^w is the concentration of free LST anions and $C_{(SAA)_{sites}}$ is the concentration of free sites in the micelles. It is assumed that each micelle is made up of a certain number of sites, each of which has n molecules of SAA accessible to one molecule of the anion. The total concentrations of SAA and LST are given by

$$C_{SAA} = n \times C_{(SAA)_{sites}} + n \times C_{LST-SAA} + CMC \quad [7]$$

$$C_{LST} = C_{LST}^w + C_{LST-SAA} \quad [8]$$

Using the definition of f from equations [3], [4] and [5], the following expression for the binding constant K_b is obtained:

$$K_b = nf / (1-f) (C_{SAA} - CMC - nf C_{LST}) \quad [9]$$

After rearrangement this equation is converted into linearized form

$$C_{LST} (1-f) = -1/K_b + (C_{SAA} - CMC)/n \times (1-f)/f \quad [10]$$

In applying equation [10], the values of f greater than 0.9 and smaller than 0.2 should be excluded, since the function is highly dependent on $(1-f)$ and $(1-f)/f$ which tends to zero or infinity as f tends to 1 or 0 ; respectively.

By plotting $C_{LST} (1-f)$ versus $(C_{LST} - CMC)(1-f)/f$, as shown in figure 3, the values of $1/n$ and $-1/K_b$ can be obtained from the slope and intercept of the straight line ; respectively. K_b and n were found to be $4.13 \pm 0.35 \times 10^5$ M⁻¹ and 2.258; respectively. The n value corresponds to the average number of surfactant molecules surrounding each molecule of LST K, the obtained value of n show that two molecules forming the site for LST K binding.

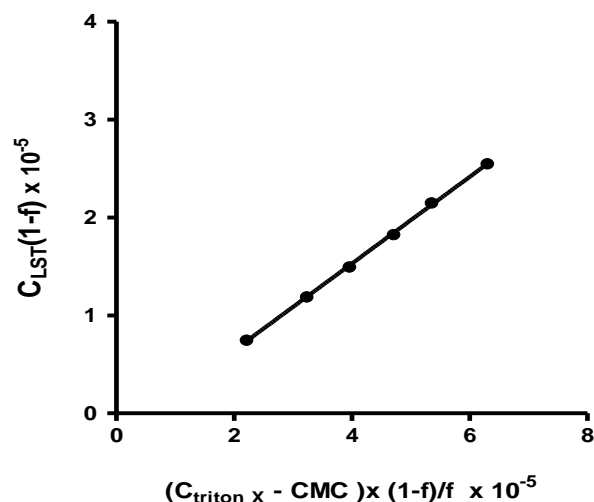


Fig. 3: The plot of $C_{LST}(1-f)$ versus $(C_{LST} - CMC)(1-f)/f$ for determination of LST-Triton X 100 binding constant.

Absorbance values obtained at $\lambda = 225$ nm can be used for the calculation of partition coefficient K_x . According to the pseudo-phase model (Chamberlain, 1987), it is defined as:

$$K_x = X_{LST}^m / X_{LST}^w \quad [11]$$

Where X_{LST}^m and X_{LST}^w are the mole fractions of LST in micellar and aqueous phase, respectively. They are related with concentrations of species in the solubilization system

$$X_{LST}^m = C_{LST}^m / C_{LST}^m + C_{Triton X 100}^m \quad [12]$$

$$X_{LST}^w = C_{LST}^w / C_{LST}^w + C_{Triton X 100}^w + n_w \quad [13]$$

Where $c_{Triton X 100}^m$ and $c_{Triton X 100}^w$ represent concentrations of Triton X 100 in micellar and monomeric states, and $n_w = 55.5$ mol dm^{-3} is the molarity of water. Under present experimental conditions $c_{LST}^w + c_{Triton X 100}^w \ll n_w$. If we express $K_s = K_x / n_w$, we get the equation

$$K_s = (C_{LST}^m / C_{LST}^m + C_{Triton X 100}^m) / C_{LST}^w \quad [14]$$

Whereas $c_{Triton X 100}$ approaches infinity, c_{LST}^m and $c_{Triton X 100}^m$ approach c_{LST} and $(c_{Triton X 100} - CMC)$. By using equations [4] and [5], equation [14] can be written in linearized form

$$1/\Delta A_{225} = 1/\Delta A_{225}^0 + 1/K_s \cdot \Delta A_{225}^0 (C_{LST} + C_{Triton X} - CMC) \quad [15]$$

Hence, K_s ($K_x = K_s n_w$) is obtained from the slope of the plot of $1/\Delta A_{225}$ versus $1/(C_{LST} + c_{Triton X 100} - CMC)$ shown in figure (4).

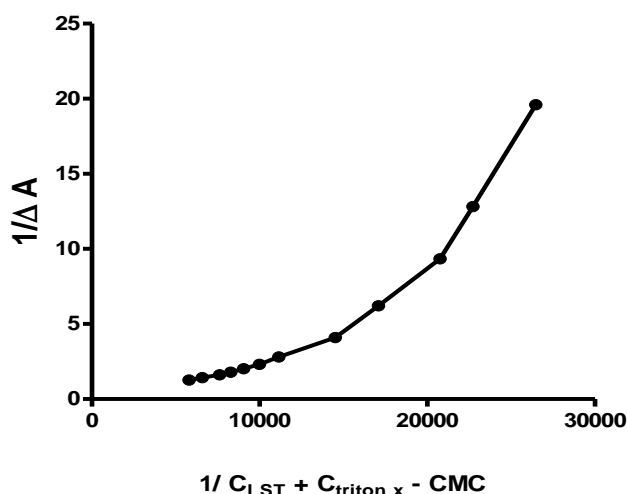


Fig. 4: The plot of $1/\Delta A_{225}$ versus $1/(C_{LST} + C_{Triton X} - CMC)$ for determination of LST-Triton X 100 partition coefficient.

The linear relation holds in a very high $C_{Triton X 100}$ region below which the curve tends to bend upwards with decreasing $C_{Triton X 100}$, the deviation being due to the approximation made for C_{LST}^m and $C_{Triton X 100}^m$

Using the values of ΔA_{225} measured in three series ($n=3$) of 43.38 μM LST K containing increasing concentrations of Triton X 100 ($1 \times 10^{-5} - 2.5 \times 10^{-4}$), from Eq. (15) the values of $K_s = 4.07 \pm 0.22 \times 10^3 M^{-1}$, i.e. $K_x = 2.26 \pm 0.12 \times 10^5$ was obtained.

From the equation $\Delta G_x = \mu_m^0 - \mu_w^0 = -RT \ln K_x$, where R ($=8.314$ $JK^{-1} mol^{-1}$) is the gas constant and T ($=298$ K) the absolute

temperature, the standard free energy change for the transfer of LST from bulk water to micellar phase $\Delta G_x = -30.54$ $kJ mol^{-1}$ is obtained.

The information about dissociation constants is necessary to choose the optimal conditions for the extraction of these drugs from body fluids, which is an essential step to develop analytical methods for their determination. Micellar systems can shift acid–base equilibria. This shift can be explained in terms of differences between the properties of the bulk solvent and of the interfacial region and perturbation of the acid–base equilibria by the electrostatic field effect of the charged interface (Jaiswal *et al.*, 2005). The study of acid–base behavior in surfactant media is important to the understanding of mechanisms of reactions in both in vitro and in vivo environments and is also useful in analytical and pharmaceutical applications (Drummond *et al.*, 1989). Different values for acid–base constants for LST K were reported in literature; 2.36 & 5.55 (Cagigal *et al.*, 2001), 3.15 (Williams *et al.*, 1996), 4.9 (Furtek & Lo, 1992) and 5.6 (Berezin *et al.*, 1973). The UV absorbance spectra of $4.34 \times 10^{-5} M$ ($20 \mu g L^{-1}$) LST K in 0.01M Triton X 100 at pH 7.4 (completely ionized species) and at pH 1.8 (completely molecular form) are shown in figure 5. The maximum difference in absorbance between the completely molecular and the completely ionized forms was obtained at 242 nm. Hence, this was chosen as the analytical wavelength at which the absorbance values of other solutions, containing similar concentrations of LST K and Triton X 100, at different pH values were recorded. The pK_a values were then calculated as a function of pH using the formula (Williams *et al.*, 1996):

$$pK_a = pH + \log [A_i - A / A - A_m]$$

Where A_i is the absorbance of the completely ionized species, A_m the absorbance of the completely molecular species, and A is the absorbance observed at different pH values.

The acidity constants were estimated to be $pK_a^{water} = 4.7 \pm 0.14$ and $pK_a^{micelle} = 3.9 \pm 0.16$. The lowering of the pK_a in micellar solutions ($\Delta pK_a = 0.8$) proves the affinity of LST K for the Triton X 100 micelle surface.

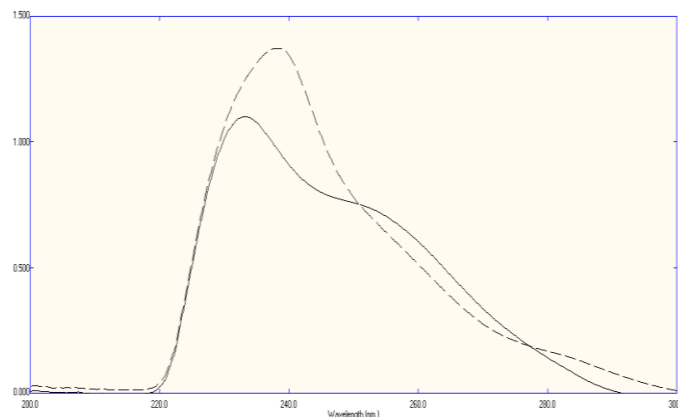


Fig. 5: The UV absorbance spectra of $4.34 \times 10^{-5} M$ ($20 \mu g L^{-1}$) LST K in 0.01M Triton X 100 at pH 7.4 (---) (completely ionized species) and at pH 1.8(—) (completely molecular form).

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 micro environmental effects of the micelles (Lee, 1978). It should be remembered that values reported in the present work are all with reference to a fixed concentration of surfactant which is well above the CMC of the surfactants. At several other intermediate concentrations or added salts/counter ions the effects are pronouncedly different (Yuanqin *et al.*, 2002). The data obtained from the study of the physicochemical interaction of LST K and Triton X 100 is summarized in table (1).

Table. 1: Parameters of the physicochemical interaction of LST K and Triton X 100 Micelles.

Parameter	pH 7.4
N	2.258
K_b (mol^{-1} L)	$4.13 \pm 0.35 \times 10^5$
R	0.9997
K_x	$2.26 \pm 0.12 \times 10^5$
K_s (M^{-1})	$4.07 \pm 0.22 \times 10^3$
ΔG_x (kJ mol^{-1})	-30.54

CONCLUSION

From the results obtained, LST K binds to Triton X 100 micelles where two Triton X 100 molecules are form the binding site. The binding constant and partition coefficient were calculated to assist in studies on drug delivery, or in micellar electrokinetic capillary chromatography and high-pressure liquid chromatography for drug quality control. The pK_a of LST K was shifted by 0.8 proving the affinity of LST K for the Triton X 100 micelle surface.

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