Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University, Bratislava, Slovak Republic

Influence of alcohols on the critical micelle concentration of heptacainium chloride. Study of local anesthetics, part 171

F. ANDRIAMAINTY, J. ČIŽMÁRIK, Z. ZÚDOROVÁ, I. MALÍK, E. SEDLÁROVÁ

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Dr. Fils Andriamainty, Faculty of Pharmacy UK, Odbojárov 10, 832 32 Bratislava, Slovakia
mouanda@fpharm.uniba.sk

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The critical micelle concentrations (CMC), of heptacainium chloride in various 0.5 M alcohols (methanol, ethanol and *n*-propanol) were determined using spectrophotometric measurements. CMC values were determined through the change in the slope when the absorbance versus surfactant concentration was plotted at 234 nm. The CMC values show that micelle formation occurred more easily in methanol than in other higher alcohols.

The effect of the presence of additives on the critical micelle concentration, CMC, of surfactants has been widely studied. Increasing attention is being devoted to the study of the incorporation or solubization of neutral molecules into micelles in aqueous solution. Some of the most studied solubizates are alcohols because of the important role they have in the preparation of microemulsions. It is generally accepted that the alcohol binds to the micelle in the surface region leading to three principal effects (Akhter and Al-Alawi 2000): (a) The alcohol molecules intercalate between the surface ionic head groups to decrease the micelle surface area per head group and increase of ionization, (b) The dielectric constant at the micellar interface decreases probably due to the replacement of water molecules in the interface region by alcohol molecules, (c) The molecular order of the interface region of the micelle changes.

The critical micelle concentrations, CMC, of the local anaesthetic heptacainium chloride in aqueous solution and solutions of n-alkanols – methanol, ethanol, n-propanol were determined by a spectrophotometry method in the UV region of the spectrum at temperature range $t = 22–35\ ^\circ C$ and $pH \approx 4.5–5$. Experimental results show (Fig.) an increase in CMC values for solutions of methanol and ethanol in comparison with aqueous solutions, for example at $T = 295.15\ K$ ($CMC \approx 3.04 \times 10^{-4}$ M), $T = 298.15$ K ($CMC \approx 3.07 \times 10^{-4}$ M), $T = 303.15$ K ($CMC \approx 3.20 \times 10^{-4}$ M), $T = 308.15$ K ($CMC \approx 3.33 \times 10^{-4}$ M). The CMC values for solutions of n-propanol are lower than for solutions of ethanol. Decrease in CMC values caused by addition of n-propanol may be the consequence of the penetration of alcohol molecules into micelles. Based on these results, we suppose a decline of the CMC values with increasing alcohol chain length.

The thermodynamic parameters, such as standard Gibbs free energy (ΔG°), enthalpy (ΔH°) and entropy (ΔS°) of micellization for methanol and ethanol solutions, were also calculated according to the phase separation model (PS_1 and PS_2) (Evans and Wightmann 1961). The equation $CMC = f(T) = A + BT + CT^2$ represents the dependence of the critical micellar concentrations upon tempera-

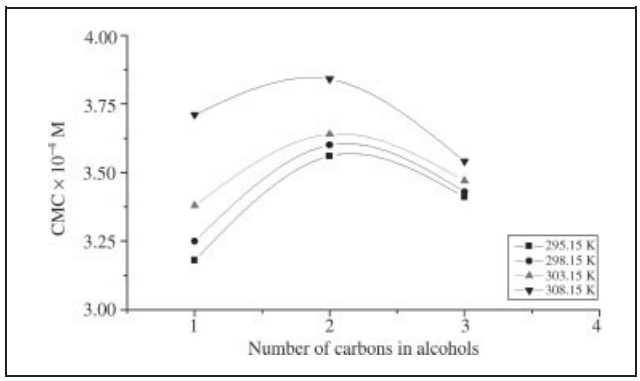

Fig.: CMC of heptacainium chloride in presence of 0.5 M alcohol solutions at different temperatures

Table: Thermodynamic parameters (ΔG^o, ΔH^o, kJ/mol; ΔS^o, kJ/mol · K^{-1}) for the local anaesthetic heptacainium chloride in presence of various alcohols (0.5 M)

Alcohol	T[K]	ΔG^o (kJ/mol)		ΔH^o (kJ/mol)		ΔS^o (kJ/mol · K^{-1})	
		PS_1	PS_2	PS_1	PS_2	PS_1	PS_2
Methanol	295.15	−19.74	−39.48	−1.39	−2.78	6.21×10^{-2}	12.42×10^{-2}
	298.15	−19.91	−39.82	−4.69	−9.38	5.10×10^{-2}	10.20×10^{-2}
	303.15	−20.12	−40.24	−10.50	−21.10	3.17×10^{-2}	6.34×10^{-2}
	308.15	−20.23	−40.46	−16.69	−33.38	1.15×10^{-2}	2.30×10^{-2}
Ethanol	295.15	−19.47	−38.94	−0.72	−1.44	6.84×10^{-2}	13.68×10^{-2}
	298.15	−19.66	−39.32	−1.48	−2.96	6.10×10^{-2}	12.20×10^{-2}
	303.15	−19.93	−39.86	−5.36	−10.72	4.80×10^{-2}	9.60×10^{-2}
	308.15	−20.14	−40.28	−9.50	−19.00	3.45×10^{-2}	6.90×10^{-2}
n-Propanol	295.15	−19.57	−39.14	−0.63	−1.26	6.42×10^{-2}	12.84×10^{-2}
	298.15	−19.76	−39.52	−1.27	−2.54	6.20×10^{-2}	12.40×10^{-2}
	303.15	−20.06	−40.12	−2.38	−4.76	5.83×10^{-2}	11.66×10^{-2}
	308.15	−20.34	−40.68	−3.57	−7.14	5.44×10^{-2}	10.88×10^{-2}

ture at pH ≈ 4.5–5, where (A,B,C) = constants of polynomial of the second degree and T = absolute temperature. Gibbs energy change can be estimated according the equation

$$\Delta G^\circ = \gamma\, RT \ln (CMC) \quad (1)$$

where R = gas constant and γ = degree of counterion binding. If $\gamma = 1$ (the anti-ions are completely ionized), if $\gamma = 2$ (the all of anti-ions are binding to micelles). The enthalpy of micellization is defined by the equation

$$\Delta H^\circ = -\gamma\, RT^2 \left[\partial \ln (CMC)/\partial T\right] \quad (2)$$

and the entropy contribution of micellization can by calculated as follows:

$$\Delta S^\circ = (\Delta H^\circ - \Delta G^\circ)/T \quad (3)$$

ΔG°, ΔH°, ΔS° values are listed in the Table.

Based on the presented results it can be concluded that

- ΔG° values are negative and slightly decline with temperature,
- Depreciations of standard molar enthalpy ΔH° are more significant at more negative values. It means that micelization process becomes more exothermic at increasing temperature,
- ΔS° values are positive and decline at increasing temperature.

Experimental

The local anaesthetic heptacainium chloride was synthesised according to Čižmárik and Borovanský (1975).

Methanol, ethanol and n-propanol used in the present work were obtained from Merck. The absorbance of the solutions were measured at various temperatures using a spectrophotometer HP 8452. Diode Array (Hewlett Packard, BRD). The pH of the medium was measured with a pH meter (Portamess 943 pH, Elekronische Messgeräte GmbH Co., Berlin). The temperature was controlled by a Thermostat (Veb ML W Prüfgerate-Werk Medingen/Sity/Freital (BRD). The critical micellar concentrations were determined by a method of Ščukin et al. (1990).

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References

Akhter MS, Al-Alawi SM (2000) Influence of alcohols on the critical micelle concentration of non-aqueous micellar solutions. Coll Surf 164: 247–255.

Čižmárik J, Borovanský A (1975) Synthesis u.v. and i.r. spectra of 2-piperidinoethyl esters of alkyloxyphenylcarbamic acids. Chem Pap 29: 119–123.

Evans DF, Wightmann PJ (1982) Micelle formation above 100 °C. J Coll Inter Sci 86: 515–524.

Ščukin ED, Percov AV, Amelinová EA (1990) Colloidal Chemistry (in Czech),1st ed., Praha Academie, p. 303–305.

School of Pharmacy, Shenyang Pharmaceutical University, Shenyang, China

Antidepressant activity of sarsasapogenin from *Anemarrhena asphodeloides* Bunge (Liliaceae)

L. X. Ren, Y. F. Luo, X. Li, Y. L. Wu

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Dr. Yingliang Wu, School of Pharmacy, Shenyang Pharmaceutical University, Wenhua Road 103, Shenyang, 110016, China
yingliangwu_sypu@yahoo.com.cn

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The aim of this study was to investigate the effects of sarsasapogenin from *Anemarrhena asphodeloides* Bunge (Liliaceae) on two experimental models of depression in rats. After a two-week treatment, sarsasapogenin markedly shortened the immobility time in the forced swimming test and decreased the number of escape deficits in the learned helplessness paradigm, however, locomotor activity was not affected.

Anemarrhena asphodeloides Bunge (Liliaceae) is a medicinal herb that has long been used as a constituent of traditional Chinese prescriptions aiming at treatment of senile dementia, epilepsy, depression and mental stress. Sarsasapogenin, 5β,20α,22α,25*S*-spirostan-3β-ol, is a major active component of *Anemarrhena asphodeloides*, which exhibits a variety of pharmacological effects such as the promotion of neurogenesis activity, antioxidative action, and improving cognitive impairment (Wang et al. 2004; Meng et al. 1999; Hu et al. 2005). However, no information is available about the antidepressant activity of sarsasapogenin. Thus, in the present study, we assessed the potential antidepressant effects of sarsasapogenin in two experimental models of depression in rats.

In the forced swimming test (FST), sarsasapogenin at the doses of 5, 15 and 45 mg/kg reduced, in a dose-dependent manner, the immobility time in the FST, resulting in a 9.3%, 20.9% and 29.5% immobility reduction compared with the control group, respectively (Table 1). The activity was comparable to the reference drug fluoxetine. The FST is the tool most widely used for assessing antidepressant activity preclinically. Most clinically active antidepressants

Table 1: The effects of sarsasapogenin on the immobility time in the forced swimming test and the number of line crossings in the open-field test in rats[a]

Treatment	Dose (mg/kg)	Immobility time (sec)	Number of line crossings
Control		169.3 ± 15.7	35.4 ± 8.24
Fluoxetine	15	110.6 ± 12.5[b]	37.0 ± 7.19
Sarsasapogenin	5	153.5 ± 13.0	36.2 ± 8.52
	15	134.0 ± 10.8[c]	34.9 ± 6.95
	45	119.4 ± 11.5[b]	32.8 ± 9.16

[a] Values are mean ± S.E.M. (n = 10)
[b] $P < 0.01$, [c] $P < 0.05$ vs. control (by ANOVA, Dunnett's t-test)