P 08

Study of ionization of montelukast in differently charged micellar solutions as biomembrane mimetic systems

Marija Popović-Nikolić[1], Slavica Oljačić[1], Katarina Nikolić[1], Gordana Popović[2]

[1]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, Belgrade, Serbia*
[2]*Department of General and Inorganic Chemistry, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, Belgrade, Serbia*

Montelukast is a leukotriene receptor antagonist indicated for asthma prophylaxis in adults as well as in pediatric patients 6 months of age and older. Because it is associated with numerous side effects, including neuropsychiatric events, it is very important to monitor its pharmacologic behavior when administered chronically. To gain better insight into the pharmacological properties of ionizable drugs, their physicochemical properties should be studied under conditions more similar to physiological, such as micellar solutions of surfactants as biomembrane mimetic systems. Montelukast is an ampholyte with one acidic (carboxyl) and one basic (quinoline nitrogen) group. In this study the effects of micellar solutions of differently charged surfactants (anionic SDS, cationic CTAB, and nonionic TX-100) on protolytic equilibria of montelukast were investigated potentiometrically. The solutions (5×10^{-4} M) were titrated with standard NaOH solution (0.1017 M) at a constant ionic strength (0.1 M NaCl) and a temperature 25°C. Experimental data were analyzed using the Hyperquad program. Due to poor water solubility, the pK_a values defining the ionization in water (pK_{a1}=4.07, pK_{a2}= 5.49), were obtained indirectly by extrapolation from the pK_a* values determined potentiometrically in the different methanol-water mixtures (40%, 50%, and 55% wt/wt). The pK_a values in 0.01M micellar solutions were determined without the use of cosolvent. Micelles contributed to the shift in protolytic equilibria of montelukast, anionic ΔpK_a up to +1.20, cationic ΔpK_a up to +0.27, and nonionic ΔpK_a up to +0.98. More pronounced effects are observed on the ionization of carboxyl group than quinoline nitrogen. A change in the distribution of equilibrium forms in a relation to pure water, can be expected in physiological conditions, in interactions of montelukast with polar or charged biomolecules.

Acknowledgments: This research was funded by the Ministry of Science, Technological Development and Innovation, Republic of Serbia through Grant Agreement with University of Belgrade-Faculty of Pharmacy No: 451-03-47/2023-01/ 200161. The authors thank the COST Actions CA18240 and CA18133 for support.