Does bioenvironment affect the ionization of drugs?

The ionization is one of the most important parameters that must be taken into account when predicting the pharmacological behavior of drugs. The ionization profile directly affects water solubility which has significant influence on drug bioavailability and distribution through biological membranes as well as absorption, distribution, metabolism, excretion and toxicity (ADMET) profile. The pK_a values of compounds having ionizable groups, defined only in aqueous solution do not give a complete insight into the ionization in the body fluids due to the possible interactions of drugs with biomolecules which can cause the shift in protolytic equilibria. More accurate estimation of the drugs equilibrium forms present in physiological conditions can be obtained by investigation of the ionization in conditions that are more similar to bioenvironmental, such as the micellar solutions of surfactants. Biomimetic nature of micellar solutions is based on structural and functional properties which are considered to mimic the most elementary membrane functions (Fig. 1). Surfactant micelles are confined systems which may influence reaction rates, products, and stereochemistry that may be different from those observed in the surfactant-free solutions.

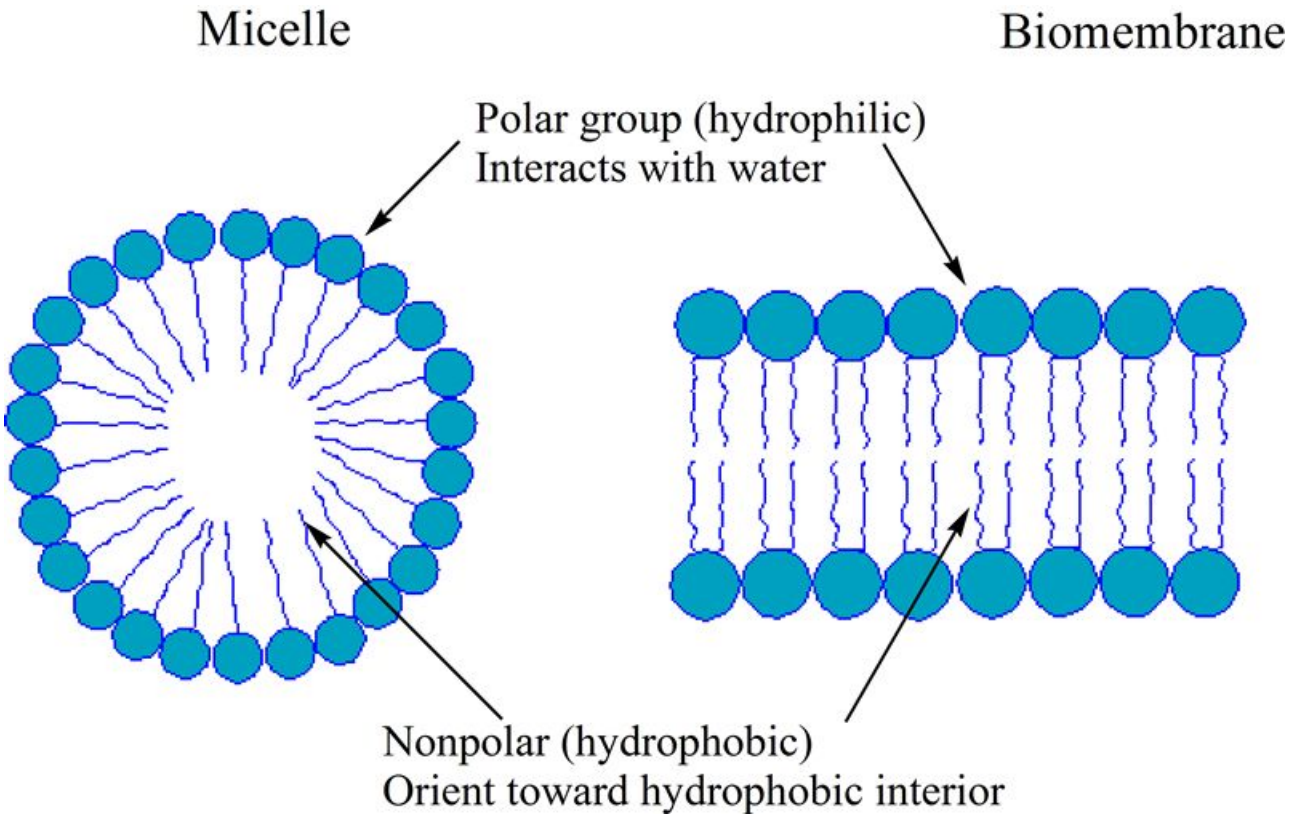

Fig. 1. Surfactant micelles vs. biomembrane.

The effects of differently charged micelles, as a membrane mimicking systems on protolytic

equilibria of some angiotensin II receptor blockers – sartans (valsartan, irbesartan, and losartan) have been investigated. From the chemical point of view, sartans represent acids or ampholytes. Irbesartan and losartan are ampholytes with acidic center (tetrazole ring) and basic center (nitrogen of the imidazole ring). Valsartan is a diprotic acid with the tetrazole ring and the carboxyl group. Ionizable groups of sartans are directly involved in the interaction with the AT1-receptor. Accurate mechanism of interaction of sartans with AT1 receptor is still not completely resolved. It is considered that not only the conformation of active form of the sartans is important for the activity, but also the ionization state in physiological conditions that can affect partitioning between plasma and biomembranes. Accordingly, the main objective of this study was to investigate the behavior of sartans in the environments with a different charge or polarity in relation to water, as well as to compare their ionization in every specific surfactant solution with ionization in water.

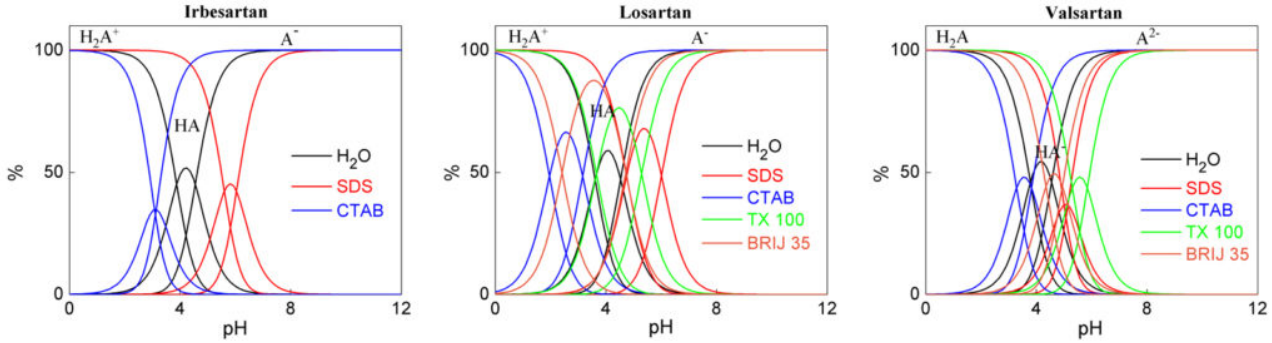

Fig. 2. The distribution of sartans equilibrium forms as a function of pH, in surfactant free (H2O) and surfactant supplied media. Irbesartan and losartan (ampholytes): H2A+, protonated form; HA, molecular form; A-, deprotonated form. Valsartan (diacid): H2A, molecular form; HA- and A2-, deprotonated form.

Investigations were performed potentiometrically in the presence and in the absence of the anionic (SDS), cationic (CTAB), and nonionic (TX-100 and Brij 35) surfactants. The effect of surfactants was estimated, based on a shift in apparent ionization constants (pK_a^{app}) determined in micellar solutions against the pK_a^w values which defines the ionization in water. The change in distribution of the equilibrium forms of the examined sartans in the presence of micelles can be clearly seen from the distribution diagrams (Fig. 2). These diagrams indicate that the shift in ionization constants expected in physiological conditions especially in pH range 3 – 5 and can be considered in terms of the potential influence on intestinal absorption and bioavailability. The largest numbers of orally administered drugs are absorbed pH 4.5, which matches the value in the proximal part of the small intestine where sartans can be included in interactions with many charged and polar biomolecules. The presence of the anionic SDS micelles shifts the equilibrium toward the formation of the cationic forms of ampholytes (irbesartan and losartan), while the cationic CTAB micelles increase the content of their anionic forms. These results point out to an increase in the ionized form of irbesartan and losartan in the presence of the positively or negatively charged biomolecules

present in small intestine. At pH 4.5, the contents of molecular forms of losartan and valsartan are increased under the influence of the nonionic surfactants. This finding indicates that an interaction of valsartan and losartan with the noncharged polar molecules can potentially affect an increase in the absorption and bioavailability of these drugs.

Gordana V. Popovi? [1], ***Marija R. Popovi?-Nikoli?*** [2]
[1]*Department of General and Inorganic Chemistry, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia*
[2]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia*

Publication

Protolytic Equilibria of Sartans in Micellar Solutions of Differently Charged Surfactants.
Gruji? M, Popovi? M, Popovi? G, Nikolic K, Agbaba D
J Pharm Sci. 2016 Aug