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Protolytic Equilibria of Sartans in Micellar Solutions of Differently Charged Surfactants

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ABSTRACT

Protolytic equilibria of irbesartan, losartan, and valsartan have been investigated in the presence and absence of differently charged anionic (sodium dodecyl sulfate), cationic (cetyltrimethylammonium bromide), and nonionic (4-octylphenol polyethoxylate and polyoxyethylene (23) lauryl ether) surfactants. Ionization constants were determined by potentiometric titration at a constant ionic strength (0.1 M NaCl) and temperature 25°C. 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 in water. The anionic surfactant caused an increase in the pK_a^{app} values of sartans (up to 1.72 pK units), while the cationic surfactant had an opposite effect and caused a reduction in pK_a^{app} values (up to −1.44 pK units). These results point out to the fact that the ionizable groups of sartans are involved in electrostatic interactions with the charged surface of the ionic micelles. Shift in the pK_a^{app} values in the presence of nonionic surfactants (from −0.86 to +1.30) is a consequence of the interactions of drugs with the hydrophilic palisade layer. Significant changes in the distribution profiles of the equilibrium forms (from −44% to +80%) are observed at the biopharmaceutically important pH 4.5 value and can be considered in terms of the potential influence on intestinal absorption and bioavailability.

Introduction

Angiotensin II receptor blockers also known as sartans represent an important class of drugs that act as competitive and selective antagonists of angiotensin II at the angiotensin AT_1 receptors.[1] Angiotensin II is a potent vasoconstrictor and the primary vasoactive peptide of the renin-angiotensin system, which plays an important role in the pathology of many cardiovascular diseases. Sartans reduce pressor effect of angiotensin II and cause the pharmacological effect of lowering blood pressure. Therefore these drugs are used in the treatment of hypertension as well as in the treatment of cardiac insufficiency, myocardial infarction, and diabetic nephropathy.[2] Accurate mechanism of interaction of sartans with AT_1 receptor is still not completely resolved. It is considered that the interaction takes place in a 2-step process, which includes spontaneously inserting into the membrane, and then lateral diffusion to the relevant transmembrane domain.[3-5] These data suggest 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.

Most of the pharmacologically active substances in their chemical structures contain weak acidic and basic groups that partly and gradually ionize in aqueous solution until they establish equilibria between molecular and ionized forms (cationic, anionic, zwitterionic) which may express different physicochemical and pharmacokinetic properties. A degree of ionization of each compound can be predicted for any pH value of the solution based on its pK_a value.[6] Even at very early stages of the drug discovery, research and development in various fields of pharmacy are unfeasible without knowing the pK_a values of the drugs.[7] The ionization profile directly affects water solubility of the drug which is important for the analysis of a drug and its biopharmaceutical characterization. Determination of the pK_a values of drugs is particularly significant for the prediction of their behavior under physiological conditions and an evaluation of drug bioavailability and distribution through biological membranes.[8,9]

After application, the drug has to pass through many biological membranes in order to reach the target site of action. In that way, it

Abbreviations used: Brij 35, polyoxyethylene (23) lauryl ether; CTAB, cetyltrimethylammonium bromide; SDS, sodium dodecyl sulfate; TX-100, 4-octylphenol polyethoxylate.

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can be involved in various physicochemical and biological interactions with biomolecules present under physiological conditions. Consequently, bioenvironment can cause changes in protolytic equilibria and ionization might be different from that in an aqueous solution. For this reason, the physicochemical parameter values defined exclusively for the aqueous solution are not sufficient for an accurate estimation of drug behavior in physiological conditions. A better insight could be provided by the determination of the pK_a value in an environment with the properties more similar to biological ones. Surfactant micelles have been used as simplified systems of biomembranes, although cell membranes characterize with a very complex structure responsible for the control of biological processes.[10-14]

Biomimetic nature of micellar solutions is based on structural and functional properties which are considered to mimic the most elementary membrane functions. Due to their amphiphilic properties, the molecules of surfactants are able to self-associate in a manner analogous to membrane phospholipids contributing to the compartmentalization of the molecules and reactions like in biological cells. Surfactant micelles are considered as confined systems which may influence reaction rates, products, and stereochemistry that may be different from those observed in the surfactant-free solutions.[10,15]

Micelles express a solubilizing effect on the compounds sparingly soluble in water. Reversible interactions between hydrophobic drugs and the micelle lead to the formation of a stable solution with the reduced thermodynamic activity of the solubilized compound.[16] It has been shown that specific microenvironment formed in a micellar solution may affect spectral characteristics,[17] the acid-base properties,[18,19] and isomerization[20] of solubilized drugs as well as membrane permeability thereof.[21] Depending on their hydrophilic or lipophilic properties, the molecules of drugs can be solubilized in the hydrophobic interior or on the hydrophilic surface of the micelles. The nature of the drug-micelles interactions which involve their hydrophilic and lipophilic parts is important for the prediction of complex biological processes such as the transport of drugs through the cell membrane.[22,23] Drugs with complex chemical structures can be involved in various interactions with the micelles and consequently it is generally impossible to predict shifts in protolytic equilibria without experimental investigations.

From the chemical point of view, sartans represent acids or ampholytes (Fig. 1). Irbesartan and losartan are ampholytes with one acidic center (tetrazole ring) and one 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 AT_1-receptor and they are an integral part of the chemical structure which is required for their pharmacological activity.[1,3] The literature survey revealed that there are not much data on determination of the pK_a values for sartans,[24-27] where in most cases only one pK_a value is experimentally determined for the molecules with 2 ionizable groups.[25-28] Also, information about an effect of micelles on the pK_a values of sartans is lacking in the literature. Only an effect of a cationic surfactant CTAB (cetyltrimethylammonium bromide) on the acid-base equilibria that includes a tetrazole ring of losartan[25] and valsartan[27] has been investigated so far.

The aim of this study was to investigate an effect of differently charged micelles, as a membrane mimicking systems on protolytic equilibria which include all ionizable groups of irbesartan, losartan, and valsartan in the pH range from 0 to 14. Investigations were performed potentiometrically in the presence and in the absence of the anionic (sodium dodecyl sulfate, SDS), cationic (CTAB), and nonionic (4-octylphenol polyethoxylate [TX-100] and polyoxyethylene (23) lauryl ether [Brij 35]) surfactants (Fig. 2). The surfactant concentration can affect the micellar phase concentrations and the micellar phase volumes, but in this study all the surfactants were applied in the same concentration. The primary objective 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.

Materials and Methods

Chemicals and Reagents

The examined compounds (losartan (2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[(2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl] imidazole, potassium salt); irbesartan (2-butyl-3-[(2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl]-1,3-diazaspiro[4,4]non-1-en-4-one); and valsartan ((*S*)-*N*-valeryl-*N*-{[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl] methyl}-valine) were kindly donated from the Medicines and Medical Devices Agency of Serbia (Belgrade, Serbia). Sodium chloride and methanol for analysis were purchased from Merck (Darmstadt, Germany). Sodium dodecyl sulfate (J.T. Baker, ≥95% purity), CTAB (Acros Organic, ≥99% purity), Triton TX-100 (Acros Organic, ≥98% purity), and Brij 35 solution (30% wt/wt in water) for biochemistry (Merck) were used to prepare micellar solutions. All solutions were prepared with double distilled water. Standard solutions of HCl and CO_2-free NaOH were standardized by potentiometry.

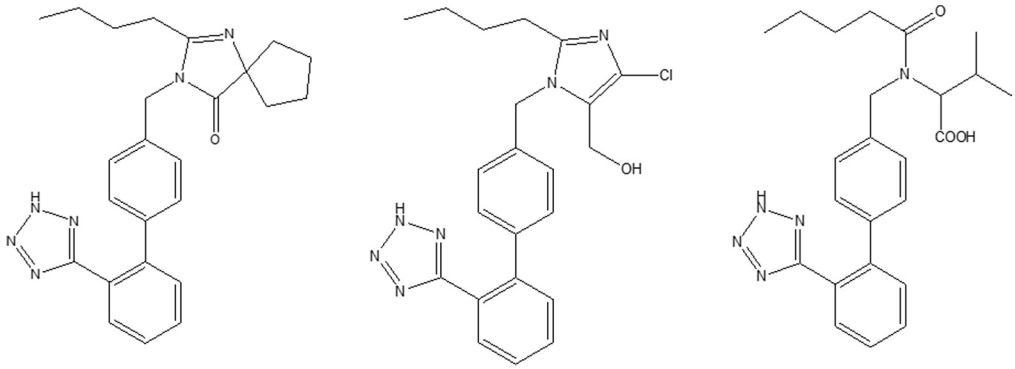

Figure 1. Chemical structures of sartans.