The Solubilization Mechanism of Benzyl Esters in Sodium Dodecyl Sulfate SDS Micelles

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Introduction

Colloidal systems have attracted the attention of many researchers in the field of pharmaceutical sciences. Being a member of the colloidal systems, Micelles, a new class of solubilization, have been utilized to increase the solubility of poorly soluble pharmaceutical compounds. To further characterize micelle and the dynamics of increasing the solubility of poorly soluble molecules, it is crucial to assess the new micelle system present upon micellar solubilization. Makerjev and Cardinal (1) studied the micromotors of benzene, several of its derivatives, Triton X-100, and the biosolute in micelles at low solubilization to surfactant ratios. They suggested a two-state model for the solubilization process in micelles. This model involves distribution between monomeric "disassociated state," which is associated with the hydrocarbon core, and a polar "solubilized state," which is associated with the micelle-water interface. Krishnan and Flanagan (2) used different series of micelles (anionic, cationic, and noncharged surfactants) to improve the solubility (β-Anterthrion antiarrhythmic drug). They were able to determine the partition coefficient of β-Anterthrion into each surfactant system. Patel and Wanstler (3) studied the effect of hydrocarbon chain length on the solubility of several hydrophobic esters in the presence of α-iodoiodoenc and CTAB micelles, they concluded that the hydrophobicity of hydrophobic esters of acetic, propionic, butyric, and hexanoic acids, in the presence of α-iodioenc, followed typical biexponential reactions and pseudo-first-order kinetics. They were able to determine the partition coefficient for each ester into the cetrimide ammonium bromide.

Materials and Methods

Kinetics study:

Hydrolysis reactions of benzyl esters were studied in both aqueous and micellar solutions of Sodium Dodecyl Sulfate SDS. Temperature of reaction was controlled by using a water bath. Buffers were used to maintain a pH of 9. Reactions and products were separated by reversed-phase high-performance liquid chromatography HPLC (Shimadzu 10A VP) using an octadecylsilica column using sodium phosphate buffer in 35 mM concentration at pH 7.4 using column oven and were detected by UV detector at 254nm.

Organic Synthesis of benzyl esters:

In a 100 mL round-bottom flask equipped with stir bar and condenser, 20 mL of hexane, 0.153 ml of carbonyl acid and 0.133 ml of alcohol were added. To this solution 1 mL of 5% phosphor acid and the solution was refluxed for 5 hours. The progress of reaction was monitored by TLC using hexamethy acetate (3:2:1:1:1). After completion of the reaction (about 24 hours), the flask was cooled down and the solution was extracted using water and diethyl ether. The organic phase was removed and the aqueous phase was washed twice each with 10 mL of diethyl ether. The combined organic phase was dried over anhydrous magnesium sulphate for a couple of hours. After filtration of drying agent and removal of volatile material under reduced pressure, the crude ester was purified by silica column chromatography (SO2, 1.5 cm × 25 cm), using hexane and then hexane: ethyl acetate (8:2 v/v) as eluent. The ester was isolated by evaporation of the solvent and yield was determined. The purity of ester was confirmed by TLC GC, and FT-IR.

Benzyl Propionate:

Isolated yield, 86% FT-IR (nm) ν max: 3034.66, 2924.16, 2943.82, 1739.16 (C=O), 1177.28 cm−1.

Benzyl Pentanoate:

Isolated yield, 77% FT-IR (nm) ν max: 3032.24, 2989.39, 2872.61, 1737.63 (C=O), 1167.80 cm−1.

Benzyl Heptanoate:

Isolated yield, 83% FT-IR (nm) ν max: 3033.38, 2956.68, 2897.81, 2789.30, 1739.73 (C=O), 1163.50 cm−1.

Benzyl Decanoate:

Isolated yield, 75% FT-IR (nm) ν max: 3033.97, 2926.38, 2838.74, 1740.10 (C=O), 1159.84 cm−1.

Results and Discussions

In order to properly study hydrolysis of benzyl esters in micelles, storage conditions were evaluated to determine the suitable micellar environment to prevent further hydrolysis prior to analysis by HPLC. Hydrolysis of benzyl acetae was studied in two environmental pH 9.22 buffer solution and pH 7% SDS micelles. Three different storage conditions (frezer -20°C, addition of acetonitrile to sample and storage at room temperature and addition of acetonitrile to sample and storage in freezer at -20°C) were all tested to determine the best suitable condition to prevent further hydrolysis of collected samples of benzyl acetae from the reaction environment until time for analysis. Collected data was compared to an immediately released sample using HPLC (UHPLC). Analyzing data by two tailed t test, results showed that there were no significant differences between the control and experimental storage conditions (p>0.05). Freezing was chosen as the optimum condition to sample storage awaiting analysis because it was less expensive, less labor intensive, and didn’t cause any precipitation of buffer.

We studied the hydrolysis of benzyl acetate, propionate, butyrate, pentanoate, and heptanoate in pH 9.22 and 4.0 pH 7.4, while varying storage conditions from 0 to 0.173 meters. Results showed a reduction in rate constants in all molecules studied as the surfactant concentrations increased. Rate constants at zero surfactant concentration decreased as the alkyl chain length of the ester group increased. As we further increased the surfactant concentrations, a reduction in rate constants was observed for all benzyl esters. The increase in surfactant concentrations generated more micelles in solution, which created a more favorable environment for the benzyl esters to move within. Values of partition coefficients were determined using pseudo phase model and were 56.9, 59.69, 135.68, and 248.01 for benzyl acetate, benzyl propionate, benzyl butyrate, and benzyl pentanoate respectively. Consequently, the increase in the number of micelles and the value of partition coefficients caused a reduced in the observed rate constants. However, partition coefficient for benzyl heptanoate was not determined from kinetics due to limited solubility in water which prevented the occurrence of the reaction in the buffer environment. As more micelles were formed, an increasing amount of benzyl heptanoate dissolved into the solution. It is well known that SDS molecules aggregate at the critical micelle concentration to form spherical micelles. We propose that benzyl esters position themselves in a linear orientation with the benzene ring pointing towards surface while the hydrophobic chains point towards the hydrophobic core of the micelle. The particular orientation increases the potential interaction with surfactant molecules. Consequently, it will enhance the solubility as well as protect benzyl esters from degradation.

Support for this hypothesis will be further explored when we conduct solubility study of each benzyl ester in surfactant solutions of 78% SDS concentration and both benzyl heptanoate and benzyl decanoate. The solubility of molecules in micelles depends on water penetration into the micelle as well as the hydrophobic core of the core. Surface tension studies need to be conducted to determine the extent of water penetration into the micelle. Several organic solvents were used (hexane, heptane and decane) to serve as a model of the hydrophobic core of the micelle. As the surface tension between water and air is the presence of surfactant fails to constant value, the surface tension between the organic solvent and water is expected to have a comparable value.

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References: