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Synthesis, biological evaluation and structure-activity relationships of self-assembled and solubilization properties of amphiphilic quaternary ammonium derivatives of quinuclidine

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ABSTRACT

This work deals with development of polyfunctional biocompatible cationic surfactant systems based on bioactive saturated bicyclic alkaloid quinuclidine. It is focused on the effect of the chemical structure of surfactants on their aggregation behavior, their physicochemical estimation of solubility of model water insoluble dye Orange OT and drugs, quercetin and rutin, microbiology and cytotoxicity. Quaternary ammonium derivatives of quinuclidine (Q-Nuc-n) with different hydrophobicity ($R = C_nH_{2n+1}$, where n = 14, 16, 18) were synthesized. Self-assembly of Q-Nuc-n was investigated by tensiometry, conductometry, spectrophotometry, fluorimetry and dynamic light scattering. The critical micelle concentration, thermodynamic and adsorption parameters at water-air interface, size and aggregation numbers of Q-Nuc-n micelles were determined. The looser packing of surfactant molecules in Q-Nuc-n micelles compared to its analogues, quaternized derivatives of 1,4-diazabicyclo[2.2.2]octane (DABCO-n), was established. The hydrophobic dye Orange OT and drugs quercetin and rutin were solubilized in micellar Q-Nuc-n solutions better than in solutions of classical surfactant CTAB and its analogue DABCO-n. Solubilization capacity of Q-Nuc-18 is 5 times higher than that of classical surfactant CTAB. Q-Nuc-18 1.95 $\mu g \cdot mL^{-1}$ has also bactericidal and fungicidal activity 2 times (against *S. aureus 209P*) and 8 times (against *B. cereus 8035*) higher than antibiotics Norfloxacin and antifungal Ketoconazole. Q-Nuc-16 has the highest bactericidal activity. It is 6 times (against *S. aureus 209P*) and 15 times (against *B. cereus 8035*) higher than the bactericidal activity value of Norfloxacin. Synthesized cationic surfactants based on quinuclidine are new multifunctional biocompatible compounds with high potential in nanomedicine and biotechnology.

1. Introduction

Nowadays the development of new multifunctional biocompatible compounds is demanded not only in industry, but also in nanomedicine and biotechnology. The supramolecular structures organized by amphiphilic compounds in solution (micelles, vesicles, bilayers, etc.) have different useful properties (adsorption, catalytic activity, solubilization etc.) [1–3]. New amphiphilic compounds and supramolecular systems play an important role in the discovery of new classes of targeted drug delivery carriers [4] and gene delivery agents [5,6]. Also, modification of commonly used nanocarriers by new amphiphilic compounds improves the characteristics and properties of nanosystems, for example, to make possible crossing of biological barriers. Due to sensitivity to various factors (temperature, pH, light, magnetic and electric fields), surfactants are very attractive for creation of nanosystems with controlled properties [7–10]. The biomimetic approach was able to enhance new biocompatible surfactants with a low critical micellar concentration (gemini surfactants) [11,12], polycationic amphiphiles [13,14], amphiphiles with natural fragments, such as sugar- [15,16], peptide- [17,18], pyrimidine- [19] containing surfactants. Environmental safety and improving the efficiency of surfactants are implemented in synthesis strategy of amino acids surfactants [20,21]. The structure of bioactive quinuclidine molecule makes it possible to combine biological activity and therapeutic action, and it is capable of creating nanocarriers at the same time [22]. Many effective therapeutic agents were synthesized in medicinal chemistry using saturated bicyclic alkaloid quinuclidine as a

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