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Antipyrine cationic surfactants capping silver nanoparticles as potent antimicrobial agents against pathogenic bacteria and fungi

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ABSTRACT

Development of effective anti-microbial agents has been hindered by the emergence of bacterial strains with multi-drug resistance. In this article, we report an efficient synthesis of silver nanoparticle (AgNP) by capping with a synthetic cationic surfactants-based antipyrine. The synthesized antipyrine cationic surfactants were characterized by FT-IR and ^{1}H NMR and their AgNPs were also delineated by TEM, DLS and UV–vis techniques. These AgNPs-capped cationic surfactants have average particle size of ~15–30 nm. These surfactants could self-assemble to form micelles in an aqueous medium and the critical micelle concentration (CMC) values as well as the surface parameters were determined at 20, 40 and 60 °C. The synthesized antipyrine cationic surfactants and their AgNPs were tested against growth of both Gram positive (*Bacillus subtilis* and *Staphyl. aureus*) and Gram negative (*Pseudomonas aeruginosa* and *E. coli.*) bacterial strains as well as fungi (*Candida albicans* and *Aspergillus niger*). It was found that the AgNPs significantly enhanced the antimicrobial activities of the synthesized antipyrine cationic surfactants. A strong structure-activity relationship was observed as a function of AgNPs functionality; providing guidance to activity prediction and rational design of effective antimicrobial nanoparticles. We propose that the antipyrine cationic surfactants-capped AgNPs can have potential bio-medical application against pathogenic bacteria.

1. Introduction

Infection diseases induced by pathogenic bacteria continue to be one of the greatest health problems worldwide. There has been constant decrease in effectiveness of antibiotics mainly due to unregulated use of antibiotics, leading to the development of multi-drug-resistant bacterial strains [1,2]. Additionally, the significant and continuous decrease in the number of approved antibiotics in the past decade has contributed to the increasingly threatening situation [3] that has resulted in an urgent need for the discovery of novel antibacterials and treatment strategies [4]. There are a number of actively pursued strategies, including searching for new antimicrobials from natural products, modification of existing antibiotic classes, and the development of antimicrobial surfactants [5]. Nanoparticles (NPs) provide versatile platforms for therapeutic applications based on their physical properties [6,7]. For example, NP size range is commensurate with biomolecular and bacterial cellular systems, providing additional interactions to small molecule antibiotics [8]. The high surface to volume ratio allows incorporation of abundant functional ligands, enabling multivalencyon NP surface to enhance interactions to target bacteria. Utilizing these characteristic features, NPs have been conjugated with known antibiotics to combat bacteria. The antibiotic moleculescan be infused with NPs via non covalent interactions [9]or incorporated on NPs via covalent bonds [10,11]. Both methods have been reported for enhanced activity against bacteria. The improved performance is proposed to result from polyvalent effect of concentrated antibiotics on the NP surface as well as enhanced internalization of antibiotics by NPs. Yet the dependence on existing antibiotics in these approaches may not be able to delay the onset of acquired resistance. The capping surfactants on NP surface can provide direct multivalent interactions to biological molecules, allowing NPs to be exploited as self-therapeutic agents [12–14].

In-spite of the fact, that silver has been utilized from time immemorial. In current years, it has been employed more extensively for numerous biomedical [15], and industrial [16] applications as it shows fantastic antimicrobial properties against an extensive variety of bacteria and fungi [17]. It is known that silver ions accomplish noteworthy decreases in microbial growth at very low concentrations, and despite the fact that the mechanism that causes this impact have not been totally illustrated yet, some researchers have attributed the cytotoxicity of silver to a few conceivable mechanisms, including the production of a lot of free radicals affecting high oxidative stress, the disturbance of cell layer integrity, or protein or DNA binding and damage to genetic material [18,19]. Recently, the biocidal properties of silver compounds

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have been upgraded through nanotechnology by means silver nanoparticles (AgNPs) which has allowed the size of AgNPs to be modularly and accurately reproduced in order to improve the stability of the colloidal emulsions as well as a controlled release of the AgNPs, obtaining a long-term antimicrobial activity and reducing unwished potential effects, among others [20,21].

Schiff bases of 4-aminoantipyrine are known for their variety of applications in the area of catalysis [22,23], clinical applications [24], and pharmacology [25]. New kinds of chemo-therapeutic agents containing Schiff bases have gained significant attention among biochemists and of those aminopyrines are commonly administered intravenously to detect liver disease in clinical treatment. The most spectacular advances in medicinal chemistry have been made when heterocyclic compounds played an important role in regulating biological activities. Heterocyclic moieties can be found in a large number of compounds which display biological activity. Antipyrine (N-heterocyclic compound) and its derivatives exhibit a wide range of biological activities and applications [26–27]. Antipyrine is a marker in the study of transfer and bio transformations of drugs in the human body [28] antipyrine metabolites are reported to show a positive correlation with plasma fibronectin level in monitoring patients with chronic liver illness (HBC, HCV and alcohol-related disease) [29]. Quaternary ammonium salts compound display antimicrobial activity against gram positive and negative bacteria, yeast and fungi. Most of quaternary ammonium salts have positive nitrogen atoms in their chemical structure. Nitrogen atom is hetero atom and carrier positive charge which lead to enhance the antimicrobial activity [30]. Several works deal with the synthesis of different cationic surfactant compounds and studied the relationship between surface activity and antimicrobial activity against wide strain of pathogenic bacteria, fungi and yeast [31–33]. In this work, we synthesized a series of antipyrine Schiff base cationic surfactants and their silver nanoparticles (AgNPs) as an antimicrobial agent. The structure-activity relationship of the synthesized surfactants capped AgNPs revealed that antimicrobial properties can be tailored through surface hydrophobicity, providinga new aspect to design antimicrobial nanomaterials. On the basis of these studies, we focused on the most potent of novel synthesized antipyrine surfactants candidate and enhance their potential by capping with AgNPs. The result showed inhibited growth of multiple strains of pathogens bacteria and fungi.

2. Materials and methods

2.1. Chemicals

4-aminoantipyrine (97%), Benzaldehyde (99.5%), chlorobenzal dehyde (97%), octyl bromide (98%), dodecylbromide(98%), hexadecylb romide(98%), silver nitrate ($AgNO_3$, 99%),and trisodiumcitrate (99%) were analytical grade chemicals were obtained from Aldrich chemical Company. All the reagents were analytical grade and used as received without further purification.

2.2. Synthesis

2.2.1. Synthesis of 4-aminoantipyrine Schiff bases (APB) and (APC)

The 4-aminoantipyrine Schiff bases were synthesized according to the following strategy. Typically, 4-aminoantipyrine (2.03 g, 10 mmol) was refluxed with benzaldehyde (1.06 g, 10 mmol) or chlorobenzaldehyde (1.40 g, 10 mmol) for 12 h in presence of ethanol (50 mL) as a solvent. After removal of the solvent under vacuum, the residue was extracted with methylene chloride and washed with water several times. The organic phase was dried over $MgSO_4$ and filtered, and, upon removal of the solvent, an analytically pure bright yellow crystalline solid was obtained APB and APCin 89 and 92% yield, respectively (Scheme 1) [34].

2.2.2. Synthesis of antipyrine cationic Schiff bases surfactant (APB8, APB12&APB16) and (APC8, APC12&APC16)

The antipyrine cationic Schiff bases surfactant were synthesized according to the following strategy. Typically, The synthesized Schiff bases (APB and APC) (5 mmol) were refluxed separately in presence of 5 mmol of the alkylbromide (octyl, dodecyl and hexadecyl bromide) individually in 50 mL of ethanol as a solvent and few drops of pipiredine as a catalyst for 24 h. After the reaction was completed, the reaction solution was concentrated to 5 mL. The residue was poured into 200 mL of absolute diethyl ether under stirring and then filtered. The precipitate was filtered, washed with absolute diethyl ether and dried to give APB8 (yield 82%), APB12 (yield 83.5%), APB16 (yield 89.5%), APC8 (yield 88%), APC12 (yield 91.5%), and APC16 (yield 92.3%) (Scheme 1).

2.2.3. Preparation of the nanostructure of synthesized antipyrine cationic surfactants with silver nanoparticles

The chemical reduction method was used to prepare silver nanoparticles solution. All solutions of reacting materials were prepared in bi-distilled water. In a typical experiment 50 mL of $AgNO_3$ solution (1×10^{-3} M) was boiled, then 5 mL of 1% trisodium citrate was added drop wise under vigorous stirring until the color changed to pale yellow. Then, heating stopped and the reaction cooled to room temperature [35]. Solutions of each prepared antipyrine cationic surfactants (APB8, APB12&APB16) and (APC8, APC12& APC16) (5 mL/5×10^{-2} M) were added drop wise during 15 min to 20 mL silver nanoparticles solution. Mixture solutions stirred continuously for 24 h until the color change. The resulting solutions with final concentration (1×10^{-2} M) labeled surfactants (APB8Ag, APB12Ag&APB16Ag) and (APC8Ag, APC12Ag& APC16Ag) were used for UV–vis absorption spectroscopy, transmission electron microscope (TEM) analysis dynamic light scattering (DLS) and for surface parameters measurements.

2.3. Characterization

The chemical structures of the synthesized antipyrine cationic surfactants were confirmed using FTIR and ^{1}H NMR spectroscopy. The FTIR analysis was done in Egyptian Petroleum Research Institute using ATI Mattsonm Infinity Series™, Bench top 961 controlled by Win First™ V2.01 Software while ^{1}HNMR was done in National Research Center using GEMINI 200 (1H 300 MHz) in $CDCl_3$·The UV–vis measurements for the solution of AgNPs and solutions of the nanostructure of the synthesized antipyrine cationic surfactants with AgNPs were carried out by UV–vis photometer. Transmission Electron Microscope (TEM) used to investigate the nanostructure of the prepared samples. A convenient way to produce good TEM samples is to use copper grids. A copper grid pre-covered with a very thin amorphous carbon film. To investigate the prepared AgNPs, the nanostructure of synthesized antipyrine cationic surfactants with AgNPs using TEM, small droplets of the liquid was placed on the carbon-coated grid. A photographicplate of the high resolution transmission electron microscopy (Type JEOL JEM-2100 operating at 200 kV attached to a CCD camera). Dynamic light scattering (DLS) was used to determine the hydrodynamic diameter of the same solution which used in TEM, and UV–vis using a Malvern Zetasizer Nano (Malvern Instruments Ltd., Worcestershire, UK). Each DLS measurement was run in triplicate using automated, optimal measurement time and laser attenuation settings. The recorded correlation functions and measured particles mobility's were converted into size distributions, using the Malvern Dispersion Software (V5.10, http://www.zetasizer.com/).

2.4. Surface tension measurements

The surface activity of the synthesized antipyrine Schiff base cationic surfactants and their nanostructures with AgNPs were determined from surface tension data and surface tension was measured by the platinum ring method using a Kruss K6 tensiometer. The surface