

Review Article

# Surface modification of SiO<sub>2</sub> nanoparticles for bacterial decontaminations of blood products



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## ABSTRACT

Bacterial infections can be caused by contamination of labile blood products with specific bacteria, such as *Staphylococcus aureus* and *Staphylococcus epidermidis*. Hospital equipment, bio-protective equipment, delivery systems, and medical devices can be easily contaminated by microorganisms. Multidrug-resistant bacteria can survive on various organic or inorganic polymeric materials for more than 90 days. Inhibiting the growth and eradicating these microorganisms is vital in blood transfusion processes. Blood bags and other related medical devices can be improved by the incorporation of organic or inorganic nanomaterials, particularly silicon dioxide (SiO<sub>2</sub>) nanoparticles. The addition of solid organic or inorganic nanoparticles to synthetic polymers or biopolymers can provide new properties in addition to antimicrobial activity. Among these NPs, formulations composed of SiO<sub>2</sub> nanoparticles and polymers have been shown to improve the mechanical and antimicrobial properties of catheters, prosthetic inserts, blood bags, and other medical devices. SiO<sub>2</sub> nanoparticles possess several advantages, including large-scale synthetic availability, simple one-pot synthesis methods, porous structure for loading antibacterial agents, good biocompatibility, and thermal stability. Plasticized polyvinyl chloride is the main polymer, which has been functionalized by these nanoparticles. In this review, we discuss the recent advances and challenges regarding the functionalization of polyvinyl chloride by SiO<sub>2</sub> nanoparticles to hinder bacterial contaminations in blood products.

## 1. Introduction

Blood banks are responsible for ensuring the safe supply of blood products to hospitals to meet the needs of transfusion medicine. The need for blood transfusions and the selection of blood products are governed by

the treatment priority, as well as the age and sex of the patient [1]. The main constraint during transfusion is the availability of donations, where any ABO blood group incompatibility that may cause transfusion reactions should be avoided [2]. Plasma,

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platelet concentrates (PC), and red blood cells (RBCs) are obtained by centrifugation and filtration of whole blood and represent the products most frequently used in transfusion [3]. Plasma is mainly administered in cases of trauma [4], RBCs are one of the only treatments to restore tissue oxygenation [5], while PCs are mainly used to prevent or treat bleeding in patients with thrombocytopenia [6].

The volume of a whole blood donation is usually 450 mL  $\pm$ 10%, and samples undergo leucodepletion, (often by filtration) for removing the immune cells from the blood [7]. In some cases, whole blood donations have the leukocytes removed (below the limit of 5 million per unit) followed by mixing the RBCs with an additive solution and are stored in a blood bag composed of di(2-ethylhexyl) phthalate and polyvinyl chloride (PVC) [8]. The type of treatment process favored by each blood bank is chosen based on several factors, each with advantages and disadvantages [9]. Generally, donors must wait for a minimum of 56 days between donations, except for certain circumstances, which can have a negative impact on supply capacity [10]. For example, women are sometimes called upon to prolong their inter-donation time interval in response to abnormally low iron stores caused by menstruation [11]. In addition, blood donations can be collected using apheresis (a medical technology for separating the soluble and cellular components of blood) [12]. The advantage of this procedure comes from the fact that it is possible to return unwanted blood components to the donor. Moreover, apheresis allows the collection of several blood products simultaneously. In this way, the apheresis process can allow higher donation frequencies closely spaced together [13].

## 2. Bacterial contaminations of blood products

Hospital equipment, bio-protective equipment, delivery systems, and medical devices may be easily contaminated by microorganisms. Microorganisms such as multidrug-resistant bacteria can survive on various organic or inorganic polymeric materials for more than 90 days and can lead to the transmission of infectious diseases [14].

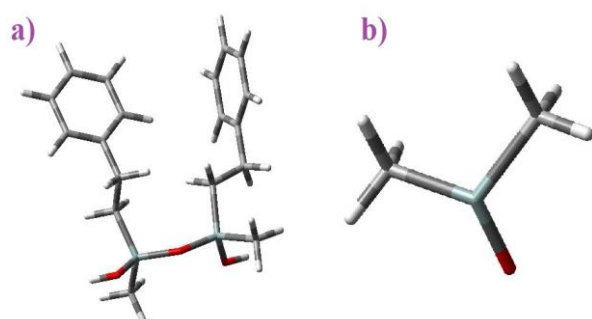
Blood banks have invested considerable time and effort in the adoption as well as the optimization of the efficiency of various contaminant detection methods. An analytical test for the detection of bacteria must not only be generic, in order to detect all possible strains but also highly sensitive to detect the presence of bacteria at very low numbers [15-18]. Recently, the standard techniques for automated bacterial detection are based on the growth of bacteria such as *Staphylococcus epidermis* and *Staphylococcus aureus* in a non-specific medium both in aerobic and anaerobic conditions. This allows the detection of bacteria at concentrations as low as 1 to 10 colony forming units (CFU) per milliliter [19-21]. Additional analytical techniques such as Real-Time Polymerase Chain Reaction (RT-PCR) for the detection of bacterial contaminants in blood products in a blood bank can be highly sensitive [22, 23]. Because it is not possible to analyze the entire volume of the labile blood product (LBP) in blood storage bags, bacterial testing can be rapidly carried out using the Matrix-Assisted Laser Desorption Ionization–Time Of Flight Mass Spectrometry (MALDI-TOF MS) technique on a small sample [24, 25].

Sending blood products to hospitals before obtaining the results of microbiological testing entails a potential risk involving the transfusion of contaminated or toxic blood products. Since the analytical process is lengthy, PCs with a short shelf life can actually be sent to hospitals before obtaining the final results to limit product losses [26, 27]. On the other hand, an analysis of risks is required and all contaminated products must be traced and removed from inventories. If any contaminated product has been transfused, medical steps must be taken to ensure patient safety [28, 29].

## 3. Antibacterial and antiadhesive coatings

Materials that make up medical devices, such as blood storage bags and catheters have gradually evolved along with the development of plastic tubes [30, 31]. Different materials or biomaterials such as thermoplastics (PVC and polyethylene), thermosetting polymers (cross-linked polyurethane, PUR), flexible elastomers (silicones and linear PUR), or cellulose can be used to fabricate catheters

[32-34]. Polyethylenes and PVC can be functionalized with various materials, such as polyglycidyl methacrylate allowing biodegradation in physiological conditions [35]. Urinary catheters are mainly based on PUR, and their properties vary depending on the nature of the additives and plasticizers used in their manufacture [36]. Moreover, silicone, polysiloxane, or polydimethylsiloxane  $[(CH_3)_2SiO]$  polymer chains (Figure 1) with different lengths and molecular weights are attractive synthetic polymers, with suitable thermal stability, resistance to physical aging, flexibility, biocompatibility, and hydrophobic properties [37-40].



**Fig. 1.** Polysiloxane (a) or polydimethylsiloxane monomers(b)(<https://pubchem.ncbi.nlm.nih.gov>).

Many approaches are available for the modification and functionalization of the surface of organic or inorganic polymers, such as cold plasma surface treatment, which has been tested to prevent the colonization of bacteria [41, 42]. The coating of hydrophobic polymers with polyethylene glycol (PEG) chains using physical or chemical bonding to form the shape of a brush or a mushroom, has been tested in recent investigations to produce or modify polymers for different medical applications [43-45]. The goal is to generate a biocompatible interface, where this inert layer acts as a barrier to prevent non-specific biological interactions [46, 47]. For instance, adding a brush-like polymer appears to minimize the adsorption of proteins or cells onto the PVC surface [48]. However, few investigations have been carried out on the effects of PVC coated with brush-like polymers when in contact with blood or blood products [46, 49]. Moreover, other polymers, such as poly(butylene adipate-co-terephthalate) prepared as a thin film filled by  $SiO_2$  NPs via a solvent casting method were

used for inactivation of *E. coli* and *S. aureus* bacteria [50]. Some research has been done on surface modification with antimicrobial peptides (AMP) as amphiphilic cationic structures, which can bind to anionic bacterial membranes by electrostatic attraction leading to bacterial death [51]. The mechanism of action of AMPs remains complex and poorly studied, and the main problem associated with the clinical use of AMPs is their possible cytotoxicity [52].

#### 4. Surface modification by $SiO_2$ NPs

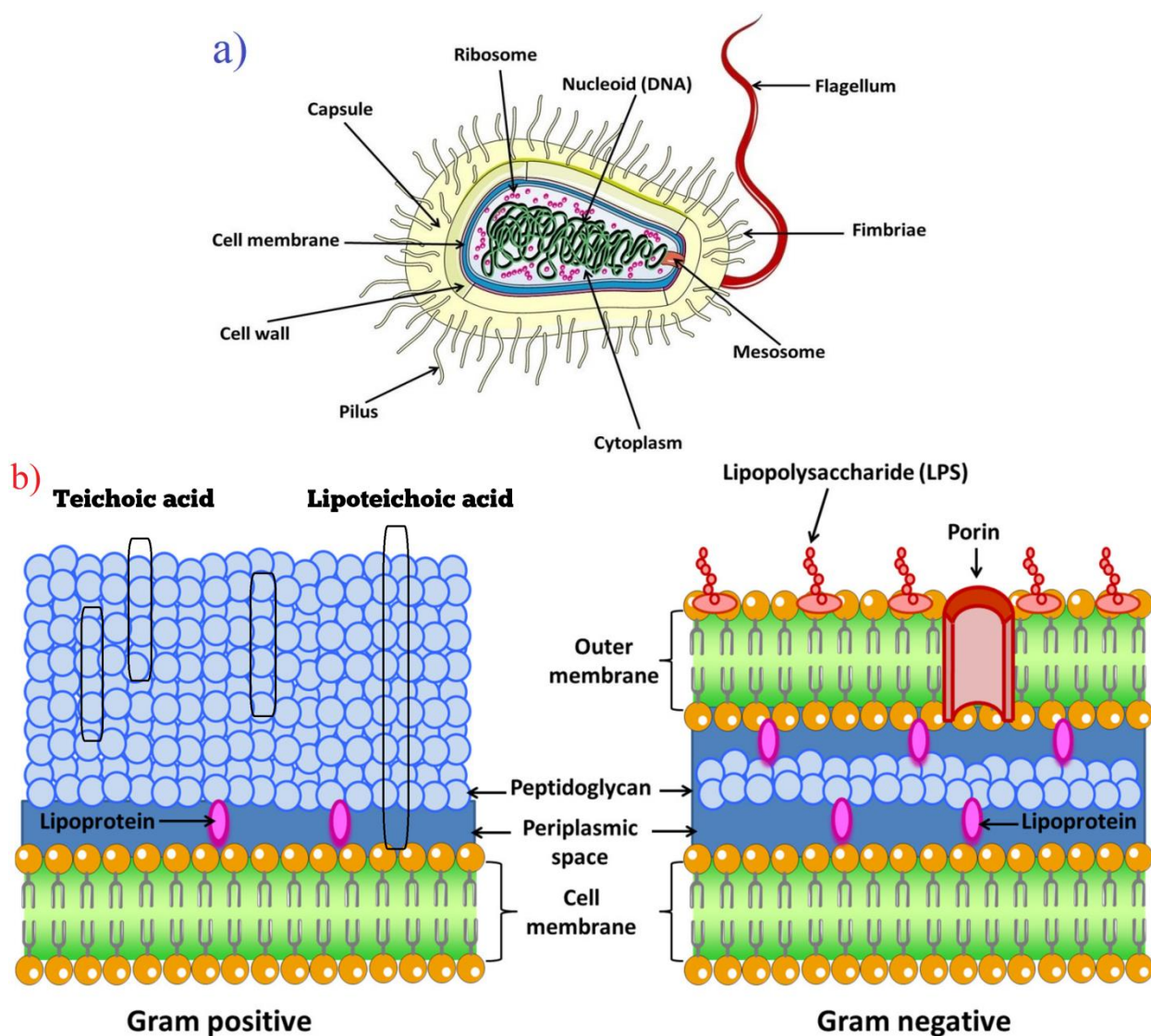
The addition of solid organic or inorganic nanoparticles (NPs) to synthetic polymers or biopolymers can provide new properties in addition to antimicrobial activity [53-56]. Among these NPs, formulations composed of silica NPs ( $SiO_2$ ) and polymers have been shown to improve the mechanical and antimicrobial properties of catheters, prosthetic inserts, blood bags, and other medical devices [57].  $SiO_2$  NPs can be prepared by three main methods, the Stober process (using a precursor of tetraethyl orthosilicate), green synthesis, and microemulsion based on water-in-oil (W/O) reverse micelles or oil-in-water micelles [58, 59]. The antimicrobial properties of  $SiO_2$  NPs are most often associated with their surface functionalization, and any process that leads to their agglomeration can present a major disadvantage [60].

Recently, several studies have described smart antibacterial biomaterials, thin films, hydrogels, and nanoparticles, which can respond to pH changes, magnetic fields, electric currents, temperature, light, as well as hydrophobic properties to be used as a medical antibacterial and antiadhesive coatings (MAAC) [61-64]. More specifically, functionalized  $SiO_2$  NPs can be incorporated into the PU matrix used during its synthesis to provide multifunctional capabilities [65]. The coating should have repellent properties so that bacteria cannot attach to the surface of materials coated by MAACs, and it can exhibit antimicrobial activity by binding to proteins associated with bacterial adhesion [66]. In the light of current knowledge on the mechanisms of action of MAACs,  $SiO_2$  NPs can bind specifically to saccharides contained in the peptidoglycan layer of bacteria, thus

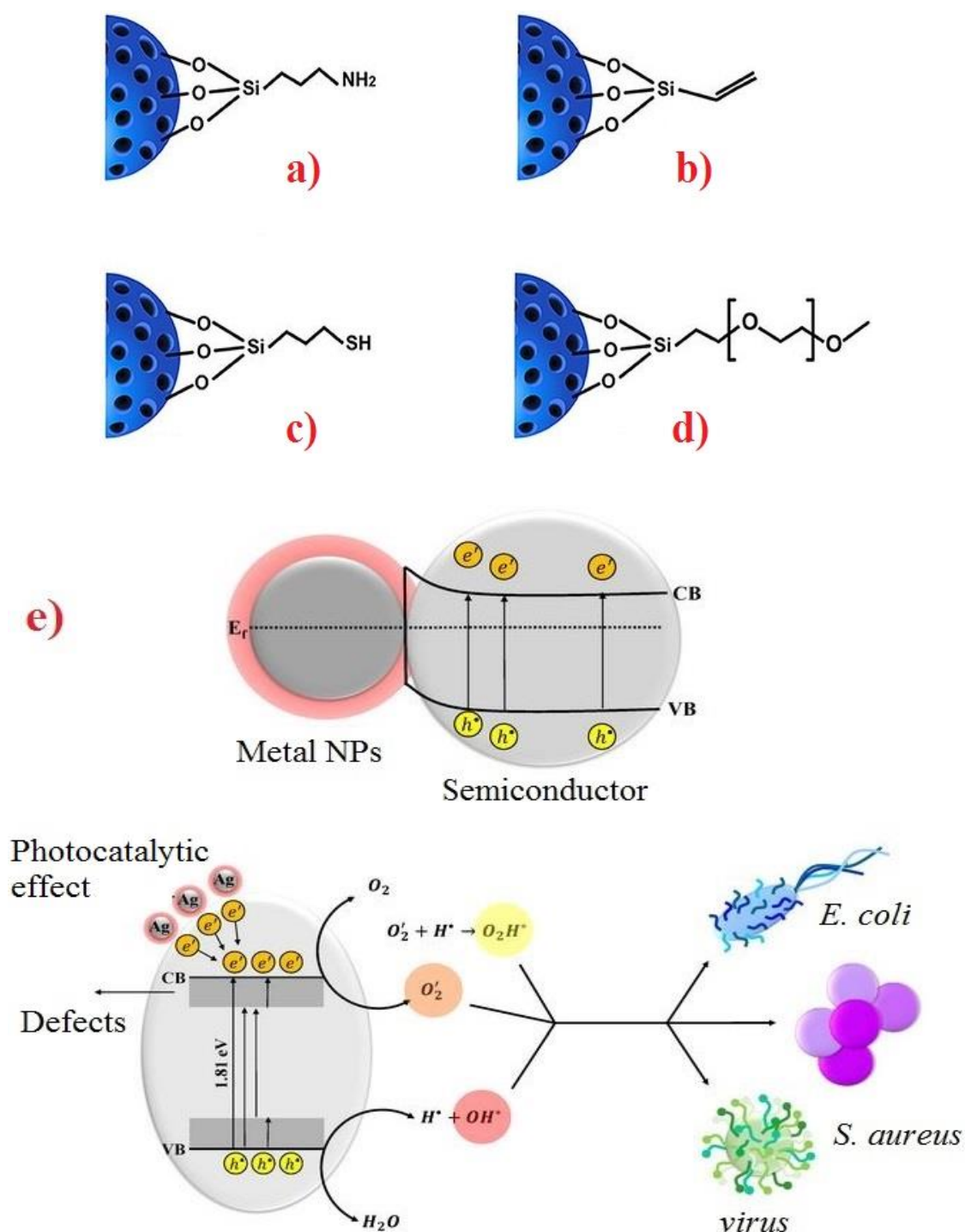


inducing an osmotic change leading to cell death [67]. It is expected that the activity of MAACs is more important for Gram-positive bacteria owing to their thicker cell wall and an accessible layer of peptidoglycan. In fact, the main structural element of Gram-positive bacteria is the peptidoglycan layer, essential for their viability, metabolism, and influx and efflux of molecules, including antibiotics [68]. The peptidoglycan layer provides rigidity to the cell, with a thickness varying between 30-100 nm. In contrast, the peptidoglycan layer of Gram-negative bacteria is only ~3 nm thick and its structure is more complex since it is located between the cytoplasmic and outer membranes [69]. As shown in Figure 2, other

components of the bacterial envelope, including capsule, fimbriae, pilus, flagellum, teichoic acid and lipoteichoic acid of Gram-positive bacteria, and lipopolysaccharide of Gram-negative bacteria could be targeted by functionalized SiO<sub>2</sub>NPs [68]. In order to achieve synergistic antimicrobial activity against bacteria or viruses, antibacterial or antiviral agents such as metals, metal oxide NPs or antibiotics can be employed to functionalize SiO<sub>2</sub>NPs to produce reactive oxygen species (ROS) that can then damage biological macromolecules (Figure 3e) [70-72]. The use of organosilane-based coupling agents is the main way to prepare different derivatives of SiO<sub>2</sub>NPs (Figure 3a-3d) [58, 73].



**Fig. 2.** a) Structure of bacterial cells; b) Structural difference between Gram-positive and Gram-negative bacteria (copyright under license <https://creativecommons.org/licenses/by/4.0/>) [68].



**Fig. 3.** Common organosilane coupling agents: (a) 3-aminopropyl-triethoxysilane; (b) vinyltriethoxysilane; (c) 3-Mercaptopropyl-trimethoxysilane; (d) methoxy-PEG-silane; (e) production of ROS upon photocatalytic activity of SiO<sub>2</sub>-Ag nanocomposites. VB and CB are the valence band and conduction band, respectively. All images have been distributed under the terms of the Creative Commons Attribution License (CC BY) [58, 73].

## 5. Conclusions

Plasticized polyvinyl chloride is the main polymer used to produce blood bags, which can be functionalized by SiO<sub>2</sub>NPs. These NPs can specifically bind to the saccharide residues of the peptidoglycan layer of the bacteria, thus inducing an osmotic change leading to cell death. Both bare and modified SiO<sub>2</sub>NPs have advantages, including large-scale synthetic availability, simple one-pot synthesis method, thermal stability, good biocompatibility, and a porous structure for loading with antibacterial agents. Several components of the bacterial envelope include the capsule, fimbriae, pilus, flagellum, teichoic acid, and lipoteichoic acid of Gram-positive bacteria, as well as the lipopolysaccharide of Gram-negative bacteria, can be targeted by functionalized SiO<sub>2</sub>NPs. To provide synergistic antibacterial activity and decrease cytotoxicity, both antibacterial agents and biocompatible materials have been employed to functionalize SiO<sub>2</sub>NPs. The application of organosilane-based coupling agents is the main route to preparing nanocomposites based on SiO<sub>2</sub>NPs combined with PVC. However, the antimicrobial properties of SiO<sub>2</sub>NPs are mostly associated with their surface functionalization, but their agglomeration in contact with blood products is an undesirable effect. Therefore, more investigations are needed to overcome these hindrances to obtain more effective antiplanktonic and antibiofilm materials composed of SiO<sub>2</sub>NPs combined polymers (specifically PVC) in medical devices suitable for blood transfusion medicine.

## Conflict of Interests

All authors declare no conflict of interest.

## Ethics approval and consent to participate

No human or animals were used in the present research.

## Consent for publications

All authors read and approved the final manuscript for publication.

## Availability of data and material

All the data are embedded in the manuscript.

## Authors' Contribution

Main draft of the manuscript was written by M.A. and revised by all authors..

## Informed Consent

The authors declare not to use any patients in this research.

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