Title: The potential of photo-deposited silver coatings on Foley catheters to prevent urinary tract infections

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Abstract

Catheter-associated urinary tract infection (CAUTI) represents one of the most common causes of morbidity and mortality. The resistance demonstrated by many microorganisms to conventional antibiotic therapies and the in- creasing health-care costs have recently encouraged the definition of alternative preventive strategies, which can have a positive effect in the management of infections. Antimicrobial urinary catheters have been developed through the photo-chemical deposition of silver coatings on the external and luminal surfaces. The substrates are exposed to ultraviolet radiation after impregnation into a silver-based solution, thus inducing the in situ synthesis of silver particles. The effect of the surface treatment on the material was investigated through scanning electron microscopy (SEM) and silver ion release measurements. The ability of microorganisms commonly associated with urinary tract infections was investigated in terms of bacterial viability, proliferation and biofilm development, using Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis as target organisms. The silver coatings demonstrated good distribution of silver particles to the substrate, and proved an effective antibacterial capability in simulated biological conditions. The low values of silver ion release demonstrated the optimum adhesion of the coating. The results indicated a good potential of silver-based antimicrobial materials for prevention of catheter-associated urinary tract infection.

1. Introduction

The urinary tract is a sterile environment in healthy people, and rep- resents one of the most susceptible sites for bacterial infections in the human body [1]. Urinary tract infections (UTIs) are one of the most common nosocomial infections, more commonly experienced by women than men; and approximately 80% of UTIs are associated with the presence of an indwelling urinary catheter [1–3]. Catheterisation is one of the most common modern medical procedures, where the insertion of a urinary catheter bypasses the normal host defences facilitating the entry of pathogens into the bladder [2]. The bacterial pathogens most commonly associated with catheter-associated urinary tract infections (CAUTIs) are Escherichia coli and Proteus mirabilis [4]. An infection associated with Proteus mirabilis frequently leads to blockage of catheters because of biomineralisation and formation of a crystalline biofilm through the bioconversion of urinary ammonium and other salts, causing obstruction of catheter lumen and kidney infection and septicaemia [4–6]. Klebsiella pneumoniae is a gastro-intestinal bacterium and an opportunistic pathogen associated with septicaemia, pneumonia, urinary tract infections, and meningitis, and can persist within the urinary tract despite appropriate antibiotic treatments [7]. Colonisation by Pseudomonas aeruginosa and Candida spp. may also be observed in patients undergoing prolonged catheterizations [4]. After long-term use, monobacterial biofilm formation has been observed to occur, some- times with multi-drug resistant organisms, on many urinary devices [8]. Bacteria have been shown to colonise the catheter surface and form a biofilm on both the internal (intraluminal) and external (extraluminal) surfaces of the catheter, suggesting that intervention strategy must ad- dress the issue of reducing or preventing bacterial colonisation on both surfaces [9,10]. Prolonged catheterisation is the most important risk factor associated with CAUTI, and the formation of biofilm plays a central role in the pathogenesis of CAUTIs [11]. Biofilms are heterogeneous structures composed of an accumulation of microorganisms and their extracellular products forming a structured community on a surface [12, 13]. These biological structures are difficult to eradicate because of biofilm-specific mechanisms of tolerance and drug resistance, with the cells and associated materials able to persist on bladder epithelium de- spite the removal of the catheters [13, 14]. The increasing reports of antibiotic resistance amongst members of the normal human microbiota has been shown to exacerbate the recalcitrance of bacterial biofilms on medical devices, limiting available therapeutic options. This is a serious medical and public health issue that requires the application of novel approaches to prevent biofilm growth on indwelling catheters [15]. An alternative approach is the incorporation of these antimicrobial agents into biomaterials used in catheter production, thus developing a catheter surface that could inhibit the bacterial growth [16]. The lack of innovative antimicrobials released on to the pharmaceutical market in recent years has led to considerable concern from the World Health

Organization (WHO). In 2014, the WHO global report on surveillance of antimicrobial resistance outlined the possibility of mortality associated to common infections such as those induced by Escherichia coli [17]. Progress and implementation in infection control programs are necessary and require technical advances in catheter materials for prevention of biofilm formation [18]. A variety of strategies, such as the replacement of contaminated catheters, novel materials for catheter production and surface functionalization with antibacterial agents have been suggested [4,15], including rifampicin, sparfloxacin and triclosan have been proposed for impregnation of urinary catheters [4]. Currently, the use of silver in biomedical field is increasing because of its broad-spectrum antimicrobial activity demonstrated against multi-drug resistant bacteria, fungi and viruses [19,20]. At nanometric size, silver is extremely active against microorganisms due to the high surface to volume ratio [21]. In this work, silver coatings have been deposited on urinary catheters on the inner and outer surfaces through a technique based on the photo-reduction of a silver precursor. Scanning electron microscopy (SEM) and silver ion release measurements through inductively coupled plasma mass spectrometry (ICP-MS) were performed to investigate the properties of the silver coating and to determine the effect of the silver treatment of the material. The antimicrobial activity has been evaluated against the most common microorganisms responsible for CAUTI through specific microbiological characterizations aiming to simulate the biological environment of the devices.

2. Materials and methods

2.1. Preparation of samples

The focus of this study was silicone-coated Foley latex urinary catheters (18 French) designed for short-term use only (less than 30 days). They have been deposited with silver coatings by adopting a technology based on the photochemical deposition of silver nanoparticles [22]. The method involves depositing a silver solution on the surface of the material and inducing the in situ synthesis and deposition of silver particles through the UV irradiation of the wet substrate. The silver solution adopted for this specific treatment has been prepared by dissolving silver nitrate (2 w/v%) in methanol (98 v/v%) under magnetic stirring at room temperature. Pieces of catheters were impregnated with the silver solution through dip coating and exposed to a UV lamp (Jelosil) with an emission peak at 365 nm for 10 min. During the UV treatment, the samples were moved to allow the irradiation on the inner surface. Next, the catheters were washed carefully in order to remove any trace of unreacted silver salt and, then, they have been characterized.

2.2. SEM-EDX analysis

Scanning electron microscopy (SEM) (Zeiss EVO) was performed by means of a backscattering detector on sections of untreated and silver treated catheters to investigate the presence and distribution of silver particles on the outer and luminal surfaces of the device. Additional Energy Dispersive X-ray Spectroscopy EDX (Bruker) was carried out to determine the surface composition and the presence of silver on both the surfaces of the device.

2.3. Silver ion release

The release of silver ions from the silver-treated substrates in artificial urine was analysed through ICP-MS (Thermofisher iCAP-Q) at the same time points selected for the microbiological characterization. The samples (length 1 cm, average weight 0.2813 g) were incubated at

37 °C in 3 mL of artificial urine medium for 1, 3, 7, 10 and 14 days. At each time point, the samples of catheters were removed from the tubes and the artificial urine was stored at 4 °C for analysis, and were conditioned at room temperature for 1 h. Transition elements calibration standard CCS-6 and 1, 10, 50 and 100 ppb concentrations were selected for calibration. Artificial urine was used as the analytical matrix (see below for constitution), and 1% HNO3 was used for dilutions.

2.4. Microbiological characterization

All microbiological media was purchased from Oxoid Ltd. (UK), and all chemicals were purchased from Fisher Scientific (UK). All experiments were performed in triplicate. The bacterial strains used in this work were Escherichia coli NCIMB 8545, Klebsiella pneumoniae NCTC

11228 and Proteus mirabilis NCTC 11938.

2.4.1. Artificial urine medium

Artificial urine (AU) was adapted in-house upon the original work of Stickler et al. [23]. The final constitution of the stock media was as follows, for 100 mL total volume: 2.3 g sodium disulphate, 0.65 g magnesium chloride, 4.6 g trisodium citrate, 0.02 g sodium oxalate, 2.8 g potassium dihydrogen orthophosphate, 1.6 g potassium chloride, 1 g ammonium chloride, 5 g gelatin, and 1 g tryptone soy broth. Reverse osmosis water was used to constitute the medium, which was subsequently autoclaved at 121 °C for 15 min. A solution of urea and calcium chloride was also

constituted; comprising 25 g of urea and 0.65 g of calcium chloride in 400 mL of reverse osmosis water was also added. This was filter sterilized using a 0.2 µm syringe filter in a Class II microbiology hood. Next, 92 mL of the stock medium was added to 8 mL of the urea/calcium chloride solution to make the artificial urine medium. These 100 mL aliquots were prepared aseptically, sealed and stored until needed.

2.4.2. Sample preparation

Samples of untreated and treated Foley catheters were cut in to 1 cm sections using a sterile scalpel within a Class II microbiology hood. These samples were sterilized by exposure to UV irradiation at 250 nm on each side for 30 min, and then sealed in new sterile plastic bags to minimize the risk of contamination. Sterility was determined by the inoculation of replicate samples in to tryptone soya broth medium. Macroscopic growth was checked at 24, 48 and 72 h visually, and at these time points 100 µL aliquots were spread on to tryptone soya agar plates (in triplicate) and incubated for 72 h at 37 °C, with inspection for colony growth at 24, 48 and 72 h, respectively.

2.4.3. Biofilm growth

Bacterial biofilms were cultivated using an adaptation of the method of Cooper and Hanlon [24]. Briefly, 1 cm2 catheter sections were immersed in 3 mL of sterile artificial urine (AU) medium in six-well plates and inoculated with 100 µL ofa1× 106 CFU/mL of each bacterial strain, respectively. These were left to sediment at room temperature for 1 h, after which, the sections were transferred into new six-well plates containing 3 mL phosphate buffered saline (PBS), and placed onto an orbital shaker for 15 min at 120 rpm (Stuart Scientific, UK) so as to dislodge any non-adherent cells. After this time, the sections were incubated at 37 °C. At time points 3, 7, 10 and 14 days, the sections to be investigated for biofilm growth were removed and placed in fresh six-well plates containing 3 mL PBS on an orbital shaker for 15 min at 120 rpm to remove any non-adherent cells. After this time, the samples were placed into 10 mL PBS containing glass balls, and vortexed for 1 min. These samples underwent serial dilution, and spread plates were set up, and incubated at 37 °C for 24 h, when colony counts were performed. For those samples being incubated for longer time periods, the samples were also placed into 3 mL PBS and placed onto an orbital shaker for 15 min. After this time, the sections were placed into six-well plates containing 3 mL AU, and incubated at 37 °C. This wash step was repeated up until the final time point for each of the samples, respectively.

2.4.4. Preparation for scanning electron microscopy

Replicate samples were set up for each organism at each time point. Samples were fixed using 2.5% glutaraldehyde in sodium cacodylate buffer (pH 7.4) for 1 h to remove the natural water. The samples were subsequently rinsed three times in cacodylate buffer, and then dehydrated in serially increasing concentrations of ethanol (25%, 50%,

75% and two washes in 97%). Each wash lasted for 30 min, and was con- ducted at room temperature and atmospheric pressure. After sputter coating with palladium, the samples were examined using a Zeiss EVO SEM (Oxford Instruments, UK).

3. Results

3.1. Preparation of samples

The silver deposition technology adopted provided a homogeneous coating characterized by the typical darkening, changing to brown, associated to the presence of silver. This proved effective at coating all sur- faces, including the luminal surface demonstrating the successful deposition of silver.

3.2. SEM-EDX analysis

Fig. 1 demonstrates the clearly visible presence of silver particles on all the treated surfaces, as also confirmed by the EDX spectra, where the peak of silver can be observed in both the luminal and outer surface (Fig. 2, arrows). The backscattered electrons emphasize the presence of silver, due to the visible contrast associated to the different chemical composition between substrate and coating.

3.3. Silver ion release

The results obtained by ICP-MS analysis are reported in Table 1. The average values of silver ion release ± standard deviation are reported as parts per millions (ppm) for each time point.

3.4. Microbiological characterization

3.4.1. Bacterial biofilm growth on uncoated Foley catheter sections

Analysis indicated that there was a significant difference between the growth of Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis on untreated catheter samples, at each of the time points, respectively (Fig. 3). Growth of Klebsiella pneumoniae was not observed on agar plates at day three, but colonies were observed at all subsequent time points. There was a statistically significant difference in the growth profile of each organism on the uncoated catheter sections (ANOVA, F = 10.27, p = 0.005). Analysis between each time point for the same bacterial strain on both treated and untreated samples (Minitab(R), t- test, p = 0.05) revealed that the statistically significant points were for E. coli: day 3 (p = 0.312), day 7 (p = 0.097), day 10 (p = 0.032), and day 14 (p = 0.025); P. mirabilis: day 3 (p = 0.28), day 7 (p =

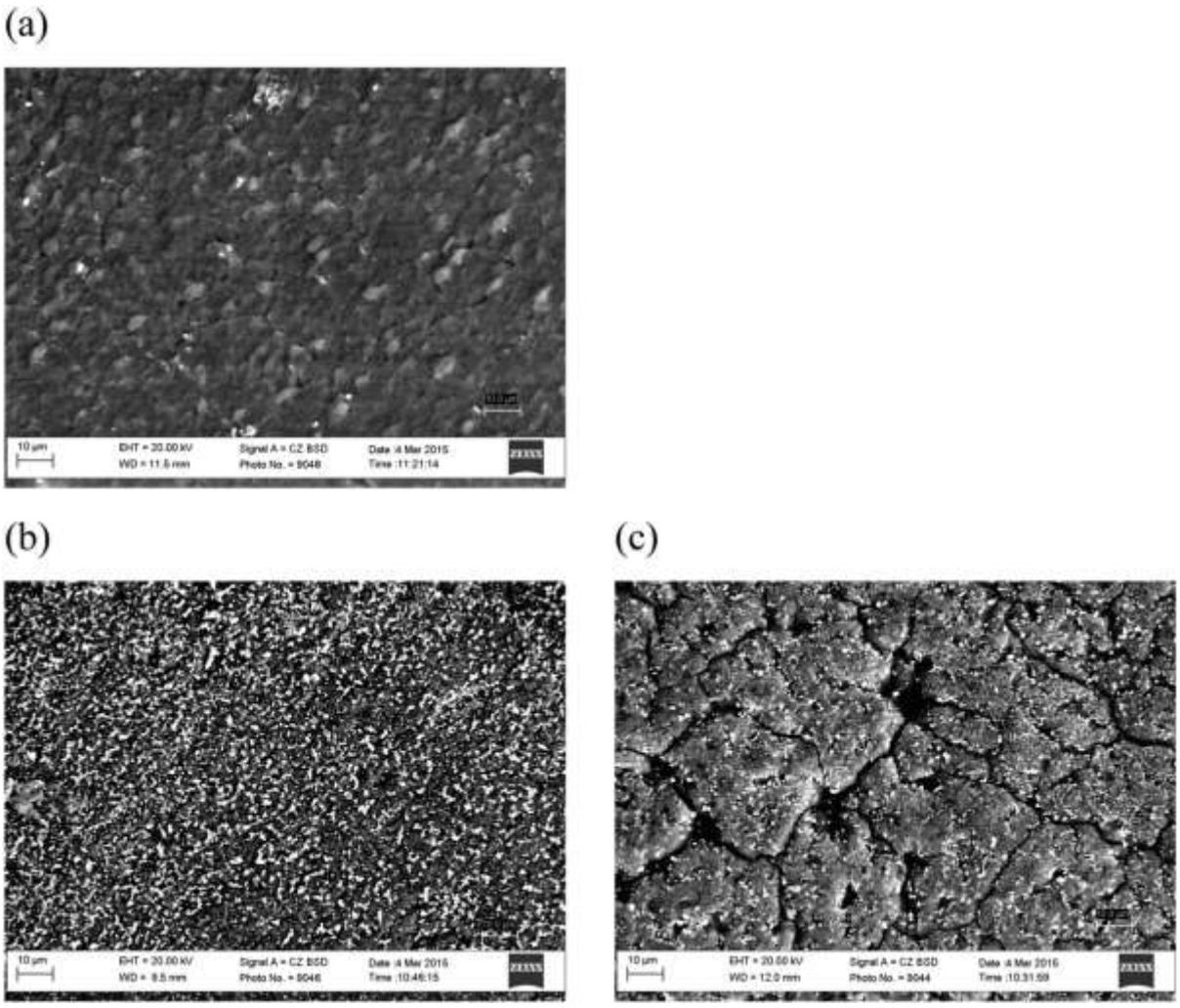

Fig. 1. SEM analysis of (a) untreated catheter, (b) external surface of the silver-treated catheter and (c) inner surface of the silver-treated catheter.

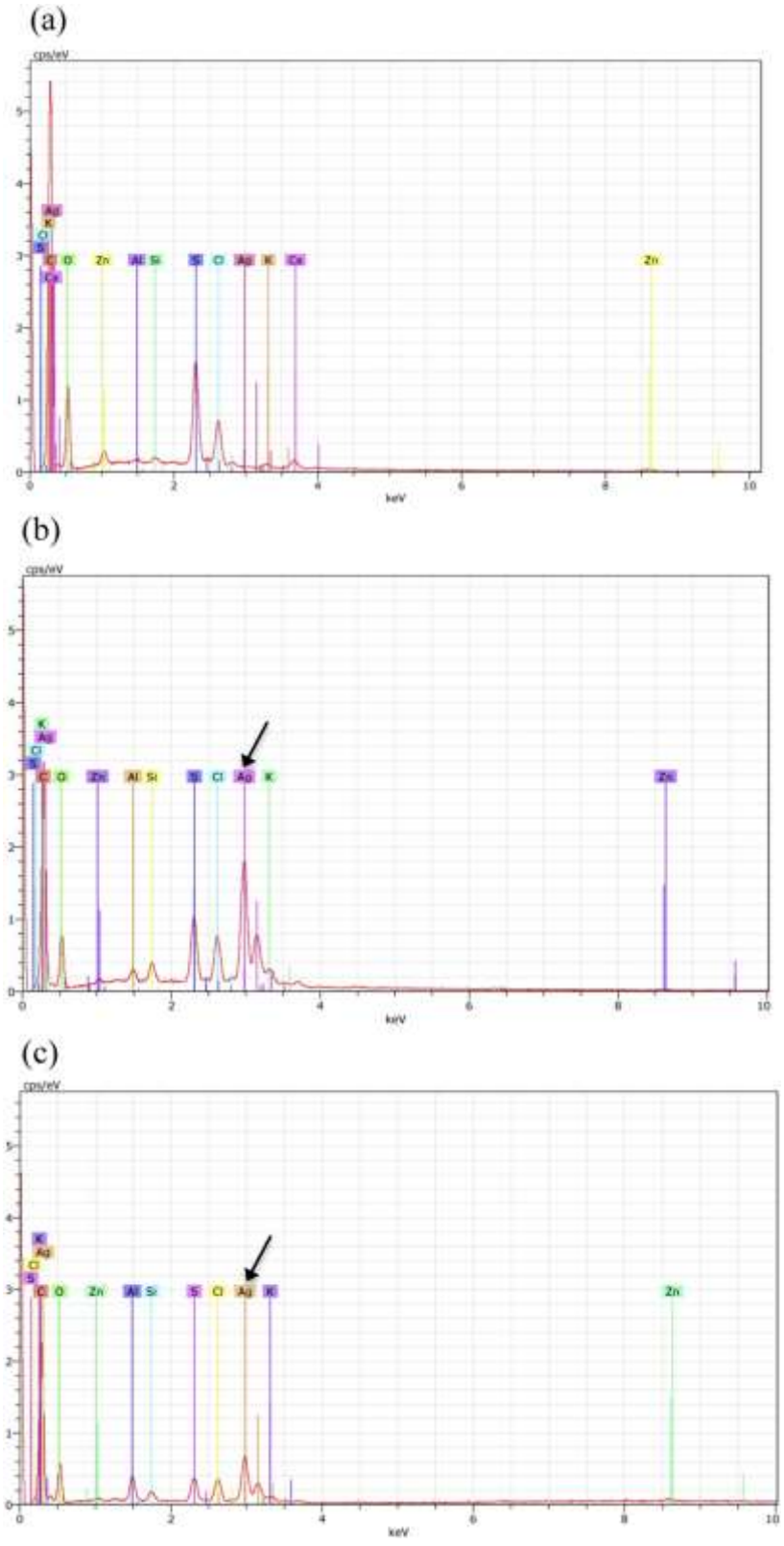

Fig. 2. EDX analyses on sections of catheter samples on (a) untreated surface, (b) external silver treated surface and (c) inner silver treated surface. The arrows indicate the position of the silver peaks.

Table 1

Average values obtained through ICP-MS analysis after incubation of silver treated catheters in artificial urine at different time points.

Time points	Silver release (ppm)
1 day	3.176 ± 0.016
3 days	4.559 ± 0.067
7 days	5.668 ± 0.053
10 days	7.746 ± 0.043
14 days	12.804 ± 0.146

0.3), day 10 ($p = 0.06$), and day 14 ($p = 0.003$); and for K. pneumoniae: day 3 ($p = 1.0$), day 7 ($p = 1.0$), day 10 ($p = 1.0$), and day 14 ($p = 0.036$).

3.4.2. Bacterial biofilm growth on coated Foley catheter sections

There was a significant difference between the growth of E. coli ($p = 0.192$), K. pneumoniae ($p = 0.189$) and P. mirabilis ($p = 0.127$) on treated catheter samples during the test period. No colonies of E. coli were observed at days 10 and 14; P. mirabilis colonies were only observed once at day 7; and K. pneumoniae colonies only observed at days 10 and 14, but not at days 3 and 7 (Fig. 4). At present, it is not known whether the reason for K. pneumoniae cells not being recovered at days 3 and 7 is due to poor adherence, or due to the efficacy of the silver at the coating concentration. It is theorised to be due to poor adherence, as colonies were able to be recovered at later time points. This could be due to the expression of a thick capsule by this strain of K. pneumoniae adjusting the binding properties to the device, but further research is needed here to elucidate this point.

3.4.3. Scanning electron microscopy of bacterial biofilms

A significant amount of crystal formation was noted in almost all of the catheter sections. In general, however, deposition was less dense on the coated sections than the uncoated ones, for all three test species (K. pneumoniae, E. coli and P. mirabilis). The exact composition of the crystals is unknown. It is likely to be struvite, but chemical testing would be required to verify this. Figs. 5 and 6 reveal biofilm formation by K. pneumoniae days 3 and 10, respectively. The greater biofilm formation was

observed on untreated samples as opposed to treated ones. SEM micrographs indicate a much greater density of bacterial cells present on the untreated surface. Unlike the other two species, however, the number of K. pneumoniae cells decreased during the test period, correlating with the spread plate data. The reduced adhesion of K. pneumoniae might be attributable to the expression of the capsule by this bacterial species. The importance of the capsule in the adherence of K. pneumoniae has been well documented. Indeed, this structure is perhaps recognized as the most important virulence factor of this bacterial species [25].

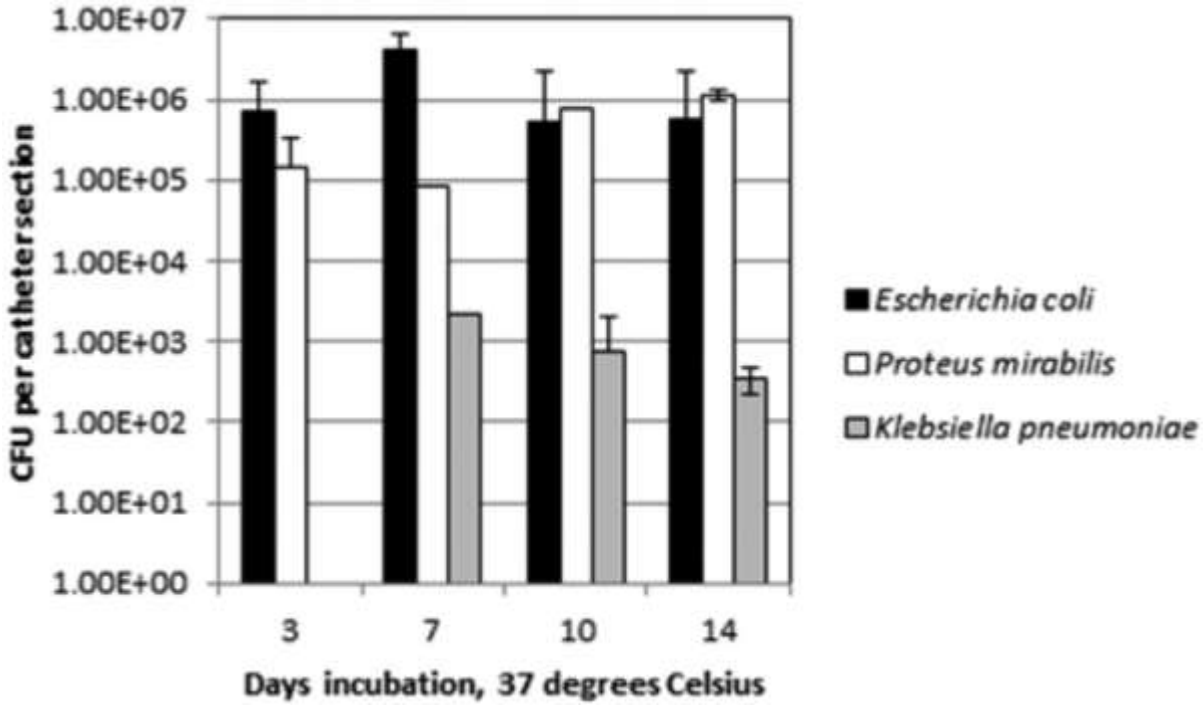

Fig. 3. The growth of Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis on untreated catheter samples. Error bars represent standard deviation from the mean data.

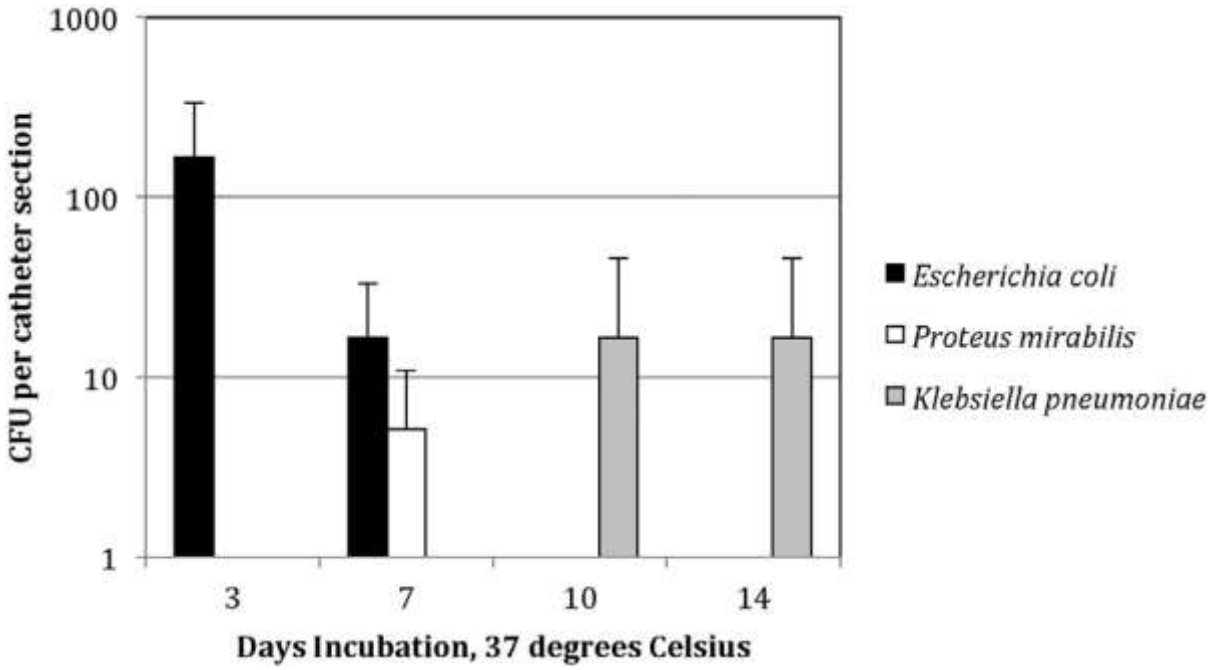

Fig. 4. The growth of Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis on treated catheter samples. Error bars represent standard deviation from the mean data.

4. Discussion

CAUTIs have been recognized as the most important cause of nosocomial infections associated with increased morbidity and mortality [1]. Antibacterial urinary tract devices to prevent UTIs are in great demand [26], and several preventive measures have been attempted including antibiotics, antiseptics and silver coatings deposited on catheters [27–29]. Chlorhexidine-loaded nanospheres sprayed on silicone surfaces have been proposed as coating of ureteral devices for sustained antibacterial release [26]; the modification of latex-based catheters by the deposition of MgF2 NPs has been analysed for prevention of bacterial colonisation and long-lasting self-sterilizing properties [30]. Also antimicrobial-impregnated catheters coated with minocycline and rifampicin have been reported as effective in reducing the incidence of Gram positive bacteriuria from 38% with non-coated catheters to 7% [31]. However, the near-universal use of antibiotics and the related risk of bacterial resistance have encouraged alternative approaches in prevention of catheter colonisation such as silver- and silver-coated hydrogel catheters [29, 31, and 32]. Catheters coated with silver alloy/hydrogel have been introduced into practice and a growing number of scientific works supports their use [29]. When compared with un- treated catheters, silver alloy catheters

demonstrated significantly reduced bacteriuria [28] and silver-hydrogel urinary catheters resulted in a 45% reduction in the incidence of catheter-associated UTIs [33]. In

1997, the University of Massachusetts Medical Center introduced silver-hydrogel urinary catheters as a mean to reduce the incidence of catheter-associated UTIs; however, this reduction did not reach statistical significance [33]. The hydrogel coating provides the catheter with the important advantage of low static and kinetic friction factors [23], which are of key importance to patient care. However, when deposited over the silver coating, the hydrogel may delay the activity of silver because of reduced ion diffusion. The mechanism of antibacterial activity proposed is associated with an initial inhibition of primary adherence due to the hydrogel hydrophilicity, followed by secondary biocidal activity of the silver coating [32,34].

Other methods have been described in literature, such as the Erlanger silver catheters developed by impregnating silicone and polyurethane with silver [35], as well as the modification of catheters through immersion in biosynthesized AgNPs suspension [36]. The devices developed in this work utilises synthesised silver clusters, which are deposited simultaneously on the outer and the luminal surface of Foley catheters for prevention of UTIs. The technology, based on a photo- chemical reaction from a covalent silver precursor to metallic silver is characterized by some advantages, such as a long-term antimicrobial capability and the excellent adhesion of the coating to the substrate [37–39]. Moreover, the process can be easily adopted to deposit silver on different natural and synthetic substrates, thus suggesting a great potential of the technology in many biomedical applications.

The work presented in this paper investigates the potential of photo- deposited silver coatings on silicone-coated latex urinary catheters, for reduced adhesion of key bacterial species linked to urinary tract infections. The first part of the work was conducted to assess the efficacy of the process to provide a homogeneous distribution of the particles on both the surfaces of the catheters. SEM-EDX analyses confirmed the success of this procedure, with the visible presence of silver particles on the substrate (Figs. 1 and 2). As expected, the presence of silver was lower onto the luminal surface than the outer, because of the lower intensity of UV radiation inside the device (Fig. 2). This effect was also assessed in a previous work, where the silver deposition was performed onto both the surfaces of haemodialysis polyurethane catheters. The amount of silver deposited resulted lower onto the inner surface, and the size of the particles deposited on the polymeric substrate was about 100–120 nm [40].

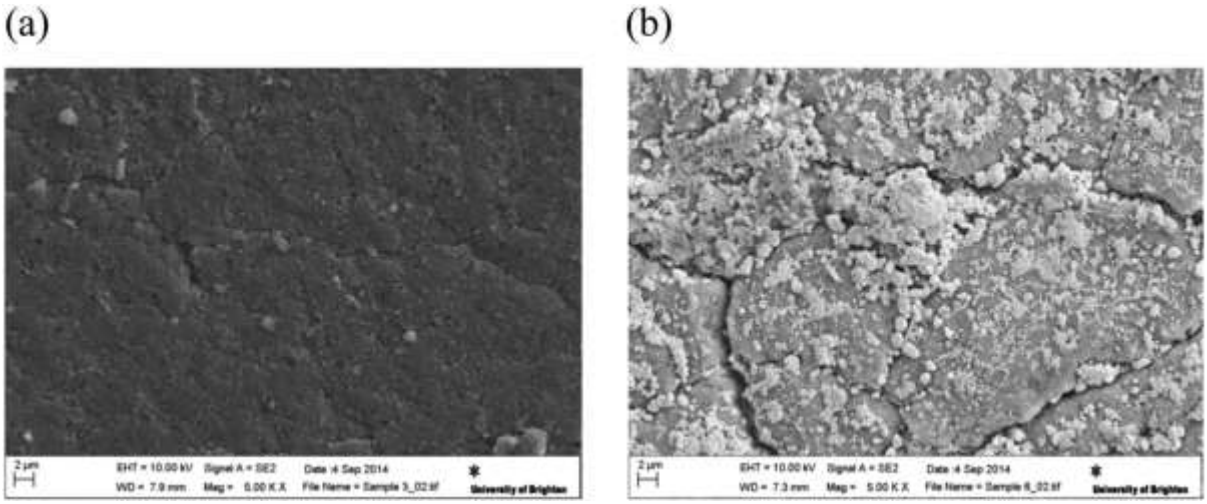

Fig. 5. Scanning Electron Micrographs of Klebsiella pneumoniae cultured on (a) treated and (b) untreated catheter sections after 3 days in artificial urine medium at 37 °C.

Several approaches have been used to prevent earliest steps of bio- film formation or to disrupt already formed biofilms; antibiotics, heparin, silver oxide and silver alloys have all been applied to the catheter surface as preventive measures [31,41,42]. Silicone is widely used as inert biomaterial for urinary devices [26]; however, silicone is more hydrophobic and rougher than acrylic and, thus presents a surface more easily able to be colonised by common human-associated microorganisms such as Staphylococcus epidermidis [43].

At the same time point's defined for microbiological characterization, the silver ion release from silver coated catheter in artificial urine was calculated. The results reported in Table 1 indicate low concentrations of silver release ranging between 3.176 ± 0.016 and 12.804 ± 0.146 ppm over the experiment. The low concentration of silver ions calculated can be associated to limited spontaneous release of silver ions in contact with aqueous media, along with possible interactions of the released silver ions with components of the artificial urine. Further, microbiological analysis indicates that the treated catheter sections appear to reduce overall coverage/biofilm mass on the catheter sections, compared with the untreated sections, when examined using SEM (Figs. 5 and 6). It must be noted that bacterial cells were not always visible on each catheter section. It is possible that the formation of what appear to be crystals on the surface is part of a biofilm, and that the cells are contained beneath the surface of those crystals. In urinary tract infections, it is known that P. mirabilis, for example, forms crystal-like biofilms which can contain live bacterial cells [44]. However, the crystals were not investigated further during this project, but could represent an appropriate

avenue for future research. Analysis of the growth profiles for each bacterial species over the fourteen day test period suggests that while all three of the test species will develop into biofilms, the treated surface is effective at reducing the rate of colonisation (Figs. 3 and 4). On the untreated catheters, data obtained both E. coli and P. mirabilis indicates that both species were able to form a biofilm on the surface, which continued to increase in size throughout the test period. On the treated surfaces, however, not only were the sizes of the E. coli and P. mirabilis biofilms significantly smaller than those on the untreated surfaces, the presence of viable cells of each species was undetectable after 7 days incubation. In contrast, the presence of K. pneumoniae cells was only observed on days 10 and 14. This suggests that each species responded to the coating differently, despite all three species being closely related. This might be related to the capsule produced by K. pneumoniae, and increased long-term survival might relate to the upregulation of capsule-associated genes. Whilst it was not measured within this study, the up- and down-regulation of capsule-associated genes would represent an interesting direction for future research.

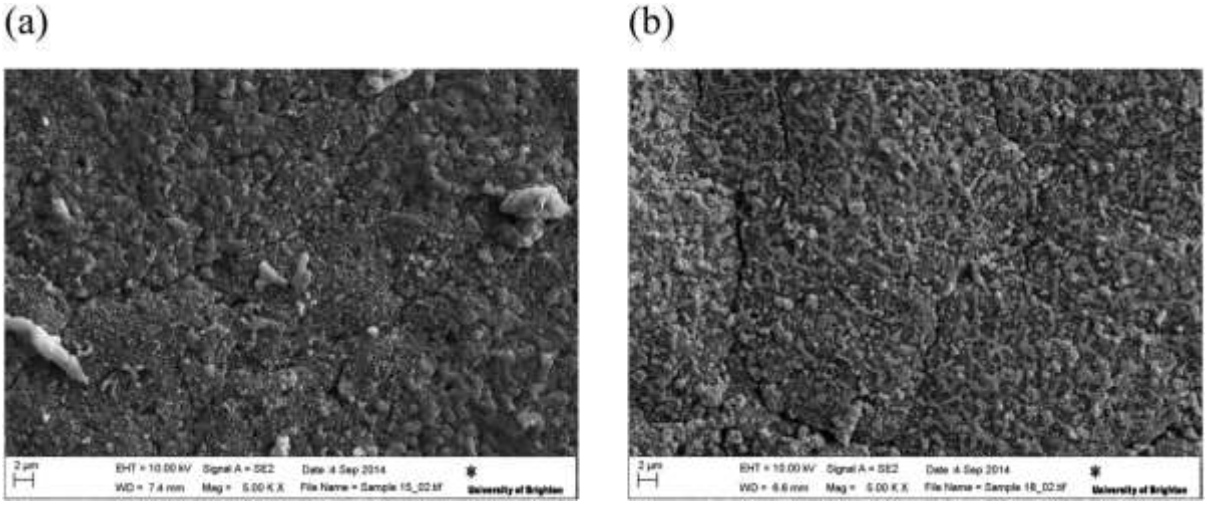

Fig. 6. Scanning Electron Micrographs of Klebsiella pneumoniae cultured on (a) treated and (b) untreated catheter sections after 10 days in artificial urine medium at 37 °C.

5. Conclusions

Urinary tract infections have been recognized as one of the most common causes of morbidity and mortality, and represent a serious concern associated with the use of indwelling urinary catheters. The in- creasing resistance of microorganisms to conventional antimicrobial therapies, along with high health-care costs, have recently encouraged the development of novel routes towards non-conventional strategies to prevent the risk of infections associated to biomedical devices [45].

In this work, novel antimicrobial silver coatings were deposited on urinary catheters. The silver deposition technology adopted is based on the in situ photo-chemical deposition of silver particles on the substrates and is characterized by nanometric size, excellent resistance even in biological environment and strong antibacterial and antifungal capability [46, 47]. The antibacterial silver treated catheters developed demonstrated good efficacy against common microorganisms responsible for urinary infections, and could be suggested as an interesting strategy for infections prevention.

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