Journal of Controlled Release 202 (2015) 57–64

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Biomaterial modification of urinary catheters with antimicrobials to give long-term broadspectrum antibiofilm activity

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ARTICLE INFO

Article history:
Received 22 September 2014
Received in revised form 26 January 2015
Accepted 28 January 2015
Available online 30 January 2015

Keywords:
Antimicrobial
Bladder
Catheter infection
Drug release
Silicone
Urinary tract

ABSTRACT

Catheter-associated urinary tract infection (CAUTI) is the commonest hospital-acquired infection, accounting for over 100,000 hospital admissions within the USA annually. Biomaterials and processes intended to reduce the risk of bacterial colonization of the catheters for long-term users have not been successful, mainly because of the need for long duration of activity in flow conditions. Here we report the results of impregnation of urinary catheters with a combination of rifampicin, sparfloxacin and triclosan. In flow experiments, the antimicrobial catheters were able to prevent colonization by common uropathogens *Proteus mirabilis*, *Staphylococcus aureus* and *Escherichia coli* for 7 to 12 weeks in vitro compared with 1–3 days for other, commercially available antimicrobial catheters currently used clinically. Resistance development was minimized by careful choice of antimicrobial combinations. Drug release profiles and distribution in the polymer, and surface analysis were also carried out and the process had no deleterious effect on the mechanical performance of the catheter or its balloon. The antimicrobial catheter therefore offers for the first time a means of reducing infection and its complications in long-term urinary catheter users.

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1. Introduction

Urethral catheters are used to drain urine from the bladder (Fig. 1). Bladder catheterization is commonly required, either for short-term bladder drainage or for long-term management of bladder dysfunction, and at least 25% of hospital patients will have a bladder catheter placed at some point in their stay. Short-term catheters are used for the temporary relief of reversible bladder voiding difficulties, for urine output monitoring or after lower urinary tract surgery and are typically used for between 1 and 14 days. Long-term catheterization may be used to manage intractable urinary problems such as chronic urinary retention or incontinence not treatable by other means, and here the aim is to keep the catheter functioning and infection-free for as long as possible but while medical opinion varies, and despite careful hygiene in handling they usually need to be changed every 4–8 weeks [1]. Catheter-associated urinary tract infection (CAUTI) is the commonest hospital-acquired infection, accounting for 40% of all nosocomial infections and over 100,000 admissions to hospital within the USA annually [2]. CAUTI rates have continued to rise in almost every care unit type [3].

The most common CAUTI pathogen is *Escherichia coli*, followed by *Proteus mirabilis* [4]. Others, such as *Klebsiella pneumoniae*, *Enterobacter* spp, enterococci and staphylococci are important but less common, and *Pseudomonas aeruginosa* and *Candida* spp may be seen in longer-catheterized patients, particularly after repeated courses of antibiotics. Increasingly, strains of *E. coli* and *K. pneumoniae* produce extended spectrum beta-lactamases (ESBL), making them insusceptible to even the newer cephalosporin antibiotics and presenting added therapeutic challenges. As in other devices, CAUTI pathogens are able to attach to the catheter material and to develop biofilms. CAUTI due to *P. mirabilis* is

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http://dx.doi.org/10.1016/j.jconrel.2015.01.037
0168-3659/© 2015 Published by Elsevier B.V.

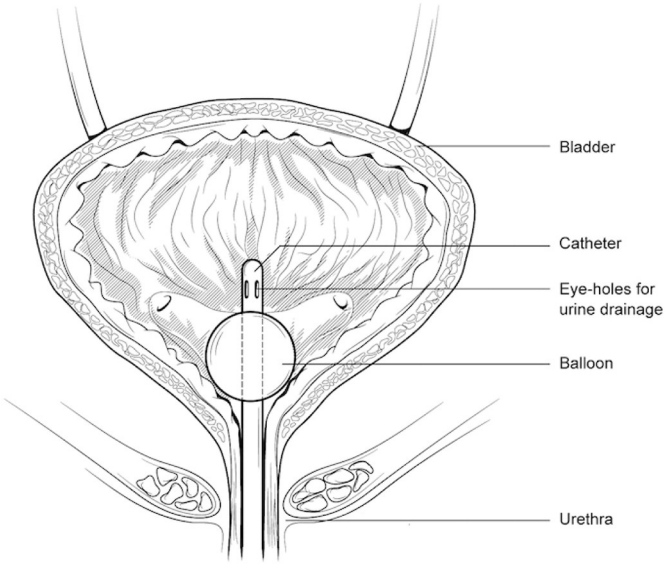

Fig. 1. Schematic of a catheterized urinary bladder, showing the Foley catheter in place. The catheter is inserted into the bladder through the urethra, and the balloon is then inflated with water using a syringe attached to a secondary channel in the catheter. The function of the balloon is to prevent the catheter from slipping out of the bladder. Urine enters the bladder from the kidneys via the ureters, and drains into the eye-holes in the catheter and then into a collecting bag.

especially important due to associated biomineralization [4,5] that can block the catheter lumen, causing obstruction and risking kidney infection and septicemia.

At least two approaches for prevention of biomaterial infection have been used. One involves modification of the biomaterial surface to reduce bacterial attachment, a pre-requisite event in biofilm development. This is usually aimed at making the biomaterial surface hydrophilic [6,7] but a class of weakly amphiphilic polymers that resist bacterial attachment have also been identified [8,9]. The second approach has been to attach active biocides such as antibiotics to biomaterial surfaces, or to impregnate them into the biomaterial itself. One example of the use of surface biocides is silver-processing using various techniques [10]. However, these have been disappointing in clinical use [11] and few "anti-biofilm" urinary catheters have reached the market. Urinary catheters containing nitrofurazone have been evaluated in a large randomized controlled clinical trial alongside silver-processed and plain catheters, and neither of these "antimicrobial" commercially available catheters showed a clinically significant reduction of infection [12]. International guidelines now state that the evidence is not sufficient to support their use in short-term (<30 days) or long-term (>30 days) users [13] and nitrofurazone catheters are now no longer available. In general, antimicrobial coatings either are depleted rapidly by urine flow, or become obliterated by a host protein conditioning film. We have previously reported an antimicrobial neurosurgical catheter produced by an impregnation process that has a long duration of activity confirmed by thousands of successful implants [14–17] and the process has been adapted for use in dialysis [18]. Our previous research on dialysis catheters, using a different antimicrobial combination, concentrated on in vitro assessment of antimicrobial activity and included investigation of potential for inflammatory reaction in the extremely sensitive peritoneal cavity. Here we report the evaluation of duration of activity of a different antimicrobial combination, drug concentrations and their distribution in the catheter material as well as their release characteristics, effect of processing on mechanical properties, particularly of the important retention balloon, and surface analysis on a novel antimicrobial catheter intended for long-term urinary drainage, with enhanced antimicrobial spectrum and duration of activity. The antimicrobials chosen, rifampicin, sparfloxacin and triclosan, were chosen for their spectrum of activity against CAUTI pathogens (rifampicin and triclosan against staphylococci, sparfloxacin and triclosan against *E. coli*, *K. pneumoniae* and *P. mirabilis*). The choice was also governed by their physicochemical characteristics: solubility in chloroform and ability to diffuse through the crosslinked silicone matrix.

2. Materials and methods

2.1. Impregnation process

The impregnation process (Fig. 2) was carried out as described previously [14]. The antimicrobials, rifampicin (Sigma-Aldrich, Poole, UK), triclosan (Ciba Speciality Chemicals, Macclesfield, UK) and sparfloxacin (Sigma-Aldrich) were chosen for their activity against the target bacteria (CAUTI pathogens) and their chemical compatibility with the impregnation process. Briefly, the antimicrobials were dissolved together in chloroform (Fisher Scientific, Loughborough, UK) to give concentrations w/v of 0.2% rifampicin, 1% triclosan and 1% sparfloxacin. Foley catheters/segments (Coloplast, Peterborough, UK) or silicone test discs 1 mm × 6 mm (Goodfellow, Cambridge, UK) were immersed in the solution for 1 h, during which the silicone swelled to approximately twice its volume. The catheters and discs were then removed and rinsed in absolute ethanol (Fisher Scientific) to remove residual solvent and drug, and allowed to dry overnight at room temperature in a current of air. During evaporation of the solvent the catheters returned to their previous dimensions (Fig. 2), leaving the antimicrobials distributed evenly throughout the silicone matrix. Separately, a series of silicone test discs was produced containing the above antimicrobial concentrations as single agents. The segments and discs were then packaged and sterilized by autoclaving at 121 °C for 15 min. The sterilization process had no significant effect on the antimicrobial activity (data not shown).

2.2. Assay of drug content and drug release profiles

Total drug content was determined by extracting catheter segments in chloroform which was then evaporated at room temperature. Drug residues were re-dissolved in acetonitrile and HPLC analysis was performed (Agilent 1090 HPLC, Agilent Technologies, Berkshire, UK) (Supplementary Method 1). The total concentration of each drug extracted from the catheter segments was calculated using peak areas from calibration curves and the total drug content per catheter was calculated. All experiments were carried out in triplicate. Calibration curves showed good linearity, with correlation coefficients (R^2) for rifampicin, triclosan and sparfloxacin of 0.9961, 0.9955 and 0.9997 respectively. To establish drug release concentrations, antimicrobial catheter segments were placed into HPLC grade water (pH 7) (Fisher Scientific) in a 37 °C incubator with constant agitation. Segments were transferred daily or every 2–4 days into fresh water over a period of 28 days. After concentration by liquid–liquid extraction using chloroform, eluates were evaporated and drug residues were re-dissolved and analyzed by HPLC. Drug release concentrations were determined from calibration curves. All tests were carried out in triplicate. Calibration curve correlation coefficients (R^2) for triclosan and sparfloxacin were 0.9998 and 0.9999.

2.3. Distribution of drugs in the polymer

The distribution of the antimicrobials at the catheter surface after impregnation and after soaking in phosphate-buffered saline (PBS, Oxoid, Basingstoke, UK) for 12 weeks with weekly changes was studied by time of flight secondary ion mass spectrometry (ToF-SIMS) depth profiling. Transmission electron microscopy, on samples prepared by focussed ion beam milling or ultramicrotomy, was used to determine the distribution of the three drugs in the polymer matrix and to investigate their particle size. Elemental analysis was performed for the presence of nitrogen, fluorine and chlorine, expected to be present in the antimicrobials but absent from the polymer (Supplementary Method 2).

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