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New antibiotic-eluting mesh used for soft tissue reinforcement

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ABSTRACT

The surgical implantation of prostheses for soft tissue repair may be followed by post-operative mesh-related infection, a significant and dramatic complication, that is treated by mesh removal. A new antibiotic-eluting mesh has been manufactured on pre-existing polypropylene prostheses using an airbrush spraying technology. Among the degradable polymers tested as coating agents and drug reservoirs, poly(ε-caprolactone) (PCL), which is deposited after heating, provides a homogeneous, regular and smooth shell around the polypropylene filaments of the mesh without dramatically altering the biomechanical properties of the new modified mesh. An anti-infective drug (e.g. ofloxacin) is incorporated into this polymeric coating giving a limited burst effect followed by sustained drug diffusion for several days. An ofloxacin-eluting mesh has demonstrated excellent antibacterial activity in vitro on *Escherichia coli* adherence, biofilm formation and inhibitory diameter, even with low drug loads. Although further in vivo investigations are required to draw conclusions on the anti-infective effectiveness of the coated mesh, the airbrush coating of ofloxacin–PCL on existing prostheses is already potentially appealing in an effort to decrease post-operative infection.

1. Introduction

Prosthetic materials are commonly used for abdominal hernia repair, pelvic organ prolapse or other soft tissue surgery. A metallic silver mesh was first introduced in the early 20th century, but prostheses have evolved greatly since in an effort to decrease post-operative complications and improve patient quality of life. Non-absorbable polymer materials were first introduced before the mid 20th century as nylon- and silicone-based prostheses. Changes made over the years have accelerated the trend to use synthetic prostheses made of polyesters (Dacron), polypropylene (PP), polytetrafluoroethylene (PTFE) and its expanded form (ePTFE) [1]. Of these, lightweight macroporous monofilament polypropylene type I, according to the Amid classification, is reported to possess many advantages over other materials [2–5].

PP materials, initially tested by Francis C. Usher in 1955 under the brand name Marlex, rapidly became one of the most popular prosthetic meshes implanted for soft tissue repair. Population aging and a trend to be over-weight have meant that soft tissue surgery is now the most common surgical procedure in western countries. Almost 1,000,000 hernias are repaired annually, and prolapse and incontinence disorders are expected to affect 10% of women in the USA [6]. Even if PP meshes are nowadays described as the "gold standard" material, modifications are nevertheless under investigation to improve the short- and long-term results. The ideal prosthesis should be inert, induce a minimal inflammatory response, and promote vascular and fibroblastic colonization to avoid material encapsulation and erosion, limit the risk of infection and promote integration with the surrounding tissue [4,6]. However, the healing process may unfortunately be delayed by bacteria that are found at approximately 90% of all implantation sites immediately after surgery. Because mesh-related infections may cause severe complications that occur weeks to years after implantation, including final mesh removal [7], the conventional procedure is to administer intravenous antibiotics intra-operatively. Bacteria encountered at the implantation site originate from the local environment and gain direct access to the surgical site during mesh insertion, and despite prophylactic sterilization and clean surgical procedures, post-operative infection rates are still significant. Various studies have demonstrated that the presence of a foreign material, such as a surgical mesh or other implantable device, dramatically increases susceptibility to infection. It has also been reported that the number of bacteria required to induce an implant-related infection is dependent upon the macroscopic and microscopic structure of the device [8]. These materials may be colonized by microorganisms that form a biofilm consisting of a mono- or multi-layer of cells embedded in an extracellular matrix. Release of the microorganisms from the

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biofilm may cause an acute, disseminated infection. An anti-infective drug-eluting mesh that slowly delivers antibiotic around the surgical site could be used to avoid bacterial contamination of the prosthesis and subsequent biofilm formation. In addition, in vitro investigations of competition between bacteria and fibroblast growth on meshes have highlighted how infected materials show poorer tissue integration [9].

Fluoroquinolones, derived from nalidixic acid, are antibacterial drugs used as first line treatment for complicated urinary tract or abdominal infections [10,11]. Quinolone drugs penetrate the bacterial wall cell through porins and inhibit cell proliferation by interfering with DNA gyrase, a topoisomerase IV involved in transcription, chromosome segregation, and replication [10]. Moreover, these antibiotics have demonstrated the promising ability to penetrate and eradicate bacterial biofilms [12].

An effective drug and local delivery system would offer several advantages over systemic administration: greater efficacy, lower drug dose required, less toxicity due to the local release of the drug, extended activity, and last but not least, less likelihood of promoting antimicrobial resistance [13,14].

As a consequence, several drug delivery systems, such as antimicrobial catheters or sutures and drug-eluting stents have been developed, obtained FDA approval, and are now widely used [15–18].

Different authors have described how the prosthesis is coated by dipping into a solution containing the drug and a polymer agent [19–22]. This coating technology has several main drawbacks in that it is difficult to produce a multi-coated device, and the technique may modify the porosity or surface morphology of the material, doubtless having an impact on the biomechanical properties of the final medical device.

The purpose of this study was to create a new antibiotic-eluting system on a pre-existing type I PP mesh used for the treatment of genital prolapse without affecting the intrinsic properties of the material. We investigated a spray coating system that uses an airbrush to produce a homogeneous and easily standardizable coating across the entire surface of the native PP mesh. Two different artificial degradable and biocompatible polyesters, poly(D,L-lactic acid) (PLA_{50}) and poly(ε-caprolactone) (PCL), were investigated as coating agents and drug delivery systems. The biomechanical properties of the modified prostheses were compared with those of the native PP type I mesh. Finally, we evaluated the antimicrobial activity of the drug-loaded mesh and used increasing quantities of ofloxacin to determine in vitro the lowest drug dose with anti-adherence and anti-biofilm effectiveness.

2. Experimental procedures

2.1. Formulation of modified meshes

Knitted PP meshes were kindly donated by Covidien (Trevoux, France). These macroporous monofilament meshes are commonly used in clinical practice for abdominal wall hernia, incontinence or prolapse surgery (large pore size >1 mm, density 35 g m^{-2}). We evaluated two different biocompatible aliphatic polyesters that we used to coat the meshes: PCL (M_n 40,000 g mol^{-1}) was purchased from Sigma (Saint-Quentin Fallavier, France), while PLA_{50} (M_n 75,000 g mol^{-1}) was a homemade product synthesized by a common ring opening polymerization method with D,L-lactide obtained from Purac (Gorinchem, The Netherlands), the process being catalyzed by zinc lactate from Sigma (Saint-Quentin Fallavier, France) [23].

The thermal characteristics of PCL and PLA were determined by differential scanning calorimetry (DSC) with measurements obtained under nitrogen and using a 10 °C min^{-1} heating rate in a Perkin-Elmer DSC6 Thermal Analyser (Waltham, MA).

The mesh was modified by spray coating using an Infinity model airbrush supplied by Harder & Steenbeck (Oststeinbek, Germany). Polymer solutions (1% w/v in acetone) were sprayed directly at a pressure of 3 bar onto the surface of the native PP meshes from a distance of 5 cm. After drying under vacuum overnight the meshes were weighed to determine the amount of polymer coating. The morphology of the coated meshes was characterized by environmental scanning electron microscopy (ESEM) at an accelerating voltage of 10 keV (Philips XL30, FEI, Hillsboro, WA) and by optical microscopy (Leica MZ6 stereomicroscope connected to an EC3 digital camera, Nanterre, France). Meshes were coated with PCL or PLA with or without heating (termed PCL or PLA Cold coating compared with Hot coating). The meshes were heated directly using a hair dryer for 10 s.

Coating homogeneity and thickness on the mesh filament were evaluated by incorporation of a fluorescent probe (Nile Red, Sigma) into the polymer solution prior to spraying. Coated meshes were embedded in OCT (Miles, Zoeterwoude, The Netherlands) and snap frozen in liquid nitrogen vapor. Sections of mesh (6 μm) were obtained using a cryomicrotome (Leica, Wetzlar, Germany) and observed under a TE300 microscope fitted with a DMX1200 digital camera (Nikon, Tokyo, Japan).

2.2. Coating impact on biomechanical properties

The effect of the coating on the mechanical properties of the meshes was determined by several mechanical tests on native and modified meshes. Each mechanical test was conducted on three samples of a standardized size and in two directions. The first direction consisted of the soft orientation and the other was perpendicular to the mesh knit.

Stress–strain experiments on 15 mm width mesh strips (clamp to clamp distance 10 mm) were performed using a computer-assisted tensiometer (Instron 4444 series, Norwood, MA) at an elongation rate of 1 mm min^{-1} until the mesh was loaded to failure. Load to failure in MPa was related to percentage mesh elongation. The elastic modulus of the mesh (E_I) was calculated over the first 15% elongation and the plastic modulus (E_{II}) was calculated from about 40% to 100% elongation.

Biomimetic tests were also conducted by loading measurements of cyclic displacement. The tensile stress of 10 20% elongations followed by 10 50% elongations of mesh length was recorded. The reduction in tensile strength was then calculated between the first and the last displacement to evaluate coating preservation. The surface integrity of the coating was also inspected by ESEM after the cyclic stress test, which provided information on the compatibility and functionality of the coated meshes for clinical applications.

A test using a Handle-O-Meter (Thwing-Albert, Berlin, Germany) instrument was performed to determine the bending rigidity properties of the different meshes. This measures the combined effects of resistance due to surface friction and flexibility of the material. Strips of meshes (2 × 10 cm) coated with PLA or PCL were compared, after heating, with native meshes in triplicate in the perpendicular direction to the mesh knit and at three points in each sample.

Briefly, meshes were placed over a 15 mm span and a penetrator engaged the sample at 159 mm min^{-1} forcing it into the span. The apparatus measured the resistance encountered by the penetrator blade as it moved into the span (expressed in grams).

2.3. Antibiotic-eluting mesh formulation

Ofloxacin ((*RS*)-9-fluoro-3-methyl-10(4-methylpiperazin-1-yl)-7-oxo-2,3 dihydro-7*H*-pyrido[1,2,3-de]-1,4-benzoxazine-6-carbox-