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Research Paper

A controlled antibiotic release system to prevent orthopedic-implant associated infections: An *in vitro* study

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ABSTRACT

A new device for local delivery of antibiotics is presented, with potential use as a drug-eluting fixation pin for orthopedic applications. The implant consists of a stainless steel hollow tubular reservoir packed with the desired antibiotic. Release takes place through several orifices previously drilled in the reservoir wall, a process that does not compromise the mechanical properties required for the implant. Depending on the antibiotic chosen and the number of orifices, the release profile can be tailored from a rapid release of the load (ca. 20 h) to a combination of rapid initial release and slower, sustained release for a longer period of time (ca. 200 h). An excellent bactericidal action is obtained, with 4-log reductions achieved in as little as 2 h, and total bacterial eradication in 8 h using 6-pinholed implants filled with cefazolin.

1. Introduction

Orthopedic medical devices have been extremely successful in restoring mobility, reducing pain, and improving the quality of life in millions of individuals each year [1]. Despite the advances achieved in orthopedic surgery, sterility levels in operating rooms, and developments in parenteral antibiotic prophylaxis, bacterial infections, mostly caused by *Staphylococcus aureus* and *Staphylococcus epidermidis*, continue to be a major complication after surgical procedures [2]. Unfortunately, most strains of those bacteria have the ability to form biofilms on medical devices becoming a major cause of refractory biofilm-associated infections. The biofilm bacteria show phenotypic resistance to antibiotics [3] and can frequently give rise to serious infections leading to prolonged hospitalization, complex revision procedures, and sometimes complete failure of the implant, requiring secondary surgery for its removal, increasing the economic burden and mortality rate [4].

Surgical site infection accounts for 15% of all nosocomial infections and, among surgical patients, represents the most common nosocomial infection [5]. Most surgical site infections are believed to be acquired during surgery [6] being a 6-h post-implantation the "decisive period" identified during which prevention of bacterial adhesion is critical to achieve a long term success of an implant [7]. Over this period, an implant is particularly susceptible to surface colonization. At extended periods, certain strains of adhered bacteria are capable of forming biofilm at the implant–tissue interface. The formation of biofilm requires the initial adhesion of bacteria to an implant surface and therefore, inhibiting bacterial adhesion is often regarded as the most critical step to prevent implant-associated infections [8]. Usually those early infections in orthopedic implants are caused by aggressive bacteria, such as *S. aureus* and gram-negative bacilli and acquired during the surgical procedure whereas delayed infections are mostly caused by hematogenously spread bacteria [9].

Almost all implants can be colonized by bacteria including coronary and biliary stents, vascular access devices, catheters, pacemakers, valves, cochlear implants, prosthetic joints, orthopedic fixation devices, breast implants and contact lenses [10]. Besides preventive measures [11], current investigation is focused on

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quorum sensing inhibition and on the development of anti-adherent surfaces to prevent them from fouling by adhesins such as polysaccharides and other components of bacterial membranes such as teichoic acids in gram-positive bacteria [12]. However, preventing bacterial proliferation and biofilm formation by manipulating the physicochemical surface characteristics is a challenging task.

Koseki et al. [13] have recently shown how different solid orthopedic implant materials (Co–Cr–Mo, Ti–6Al–4V, pure titanium and stainless steel) are rapidly colonized by bacteria and the biofilms formed on those surfaces show the same coverage rate after 2–4 h of incubation *in vitro* independently of the nature of the implant. A number of investigations have been focused on passive coatings (e.g. crystalline anatase-TiO_2, hydrophilic polymethacrylic acid, polyethylene oxide and protein resistant polyethylene glycol) [14–17] that modify the physiochemical surface properties of the implant to create anti-adhesive surfaces for bacteria. Their efficiency seems to be limited and depends on the bacterial species concerned [8]. Other promising alternatives include micro or nano-structuration of the surface [18] with the aim of mimicking nature surfaces that are less prone to bacterial adhesion (i.e., dragonfly wings, lotus leaves).

On the other hand, the use of standard medical protocols such as conventional systemic delivery of antibiotics for both prevention (prophylaxis) and treatment suffers from the drawbacks of systemic toxicity with associated renal and liver complications, poor penetration into ischemic and necrotic tissue that are typical findings on post-traumatic and postoperative tissue, and need for hospitalized monitoring [19,20]. Clearly, a more efficient way of delivering antibiotics is desirable, and this has given rise to a variety of in situ eluting devices.

The main advantage of in situ release is that it allows therapeutic dosages to be delivered at or near target locations, maximizing efficiency while minimizing systemic side effects. To achieve this, antibiotic molecules could be integrated within the device: mixed with the bone cement, adsorbed on porous structures, loaded in internal cavities or deposited on its external surface [21]. Antibiotic-doped bone cements (e.g., polymethylmethacrylate – PMMA, acrylic cement) remains a widely used material in orthopedic surgery and is effective on reducing the risk of infection [22]. However, the occurrence of infected implants is still a major concern and several important disadvantages persist. These include the induction of antibiotic resistance mainly caused by the prolonged and irregular release of antibiotic, and the fact that despite the aim of achieving early and complete release, a large proportion of the drug is not released: *in vitro* studies show that only 5–8% of the added antibiotic is released [23–25]. Finally, there is the problem of achieving the desired release rate in a reproducible way. In an ideal system, the elution rate would mainly depend on the surface area and porosity of the cement, parameters that can be controlled in the production process. However, real system rates are difficult to control and reproduce, because the antibiotic diffuses predominantly through the defects or cracks that are formed during the irregular cement drying process.

Permanent or long-duration metal implants offer additional opportunities to introduce drug delivery capabilities and have been the subject of intense investigation during the past decade [26]. Porous metals such as macroporous stainless steel [27,28] and macroporous titanium [29] were studied *in vitro* and *in vivo* showing clear advantages as the implant can provide both mechanical support and controlled local drug delivery at target tissues. In this regard, Park et al. [30] demonstrated that a hollow titanium implant perforated with microholes and loaded with a dexamethasone-based cartridge was able to provide a sustained release of this anti-inflammatory drug up to 7 weeks after implantation.

In this work, we study drug release from a new pre-filled stainless steel hollow tubular reservoir and we demonstrate the *in vitro* biocidal action of the encapsulated drug from the device. This system is presented as a model delivery device for antibiotics, with potential use in drug-eluting fixation pins for orthopedic applications. About 5% of internal fixation devices become infected, being the incidence of infection after internal fixation of 0.5–2% and up to 30%, for closed and open fractures, respectively [31]. These infections could be fought locally by antibiotic-filled hollow fixation pins, in which part of the length has been made capable of drug release. As a proof of concept, we designed four different tubular reservoirs made of hollow 316L stainless steel implants filled with antibiotic in which a variable number of through pinholes (2, 4, 6 and 8 equidistant orifices) act as gates that control the drug diffusion kinetics. The rate of drug release would then be governed by molecular diffusion through the pinholes, a process that depends on drug solubility, concentration difference between the inside and outside of the reservoir and the number and size of the orifices. In this way, uncontrollable factors (e.g. the number and size of cracks formed during the bone cement drying process,) are largely avoided, and a more robust control on the release rate can be obtained. Depending on the medical procedure requirements, release rates can be tailored by selecting drugs with the appropriate solubility in physiological media and by adjusting the number and diameter of pinholes in the implant. This model is especially relevant for clinical application in trauma because some of the currently used devices could be easily re-designed as partially hollow, drug-eluting structures without compromising their mechanical properties.

2. Material and methods

Hollow 316L stainless steel medical grade tubes were mechanized to enable their use as drug storage reservoirs and delivery implants with one open end (used to load the corresponding antibiotic) and a blind end welded on the opposite side. After loading the open end was closed with the aid of a screw PTFE cap. Four different models of implants were designed with a variable number of through pinholes (2, 4, 6 and 8 equidistant orifices), each with a diameter of 500 μm. Each implant is 2.5 cm long and 0.6 cm O.D. having a wall thickness of 1.6 mm (Fig. 1). The design of these implants allows a controlled diffusion of the desired drug from the inner space, through a posterior permeation across the corresponding orifices and then to the exterior space. For the experiments in this work, the antibiotics were loaded as a dry solid. This means that liquid from the outside had to enter the reservoir to dissolve the antibiotic before the dissolved molecules could diffuse out. In this work, the inner volume of the hollow implant (129 mm^3 when the lid on) was carefully loaded with either 100 mg of lyophilized commercial linezolid (Zyvox®, Pfizer, NY, USA) or 100 mg of commercial cefazolin powder (Cefazolina Normon®, Madrid, Spain). According to the manufacturer, each ml of the pharmacological solution of Zyvox® contains 2 mg of linezolid, 45.7 mg of glucose and 0.38 mg of sodium (as sodium hydroxide). The solution also contains sodium citrate, citric acid anhydrous, hydrochloric acid and water for injections. On the other hand, 1 g of powder Cefazolina Normon® contains 1 g of sodic cefazolin. Water solubilities for sodium cefazolin and Zyvox® are 50 and 3 mg/ml, respectively.

2.1. Kinetic studies of antibiotics release

Solubility and diffusion rate were evaluated by immersing the linezolid or cefazolin loaded implants in 200 ml of simulated body fluid (SBF) at 37 °C under stirring (30 rpm). SBF was prepared according to the method described by Kokubo et al. [32] having

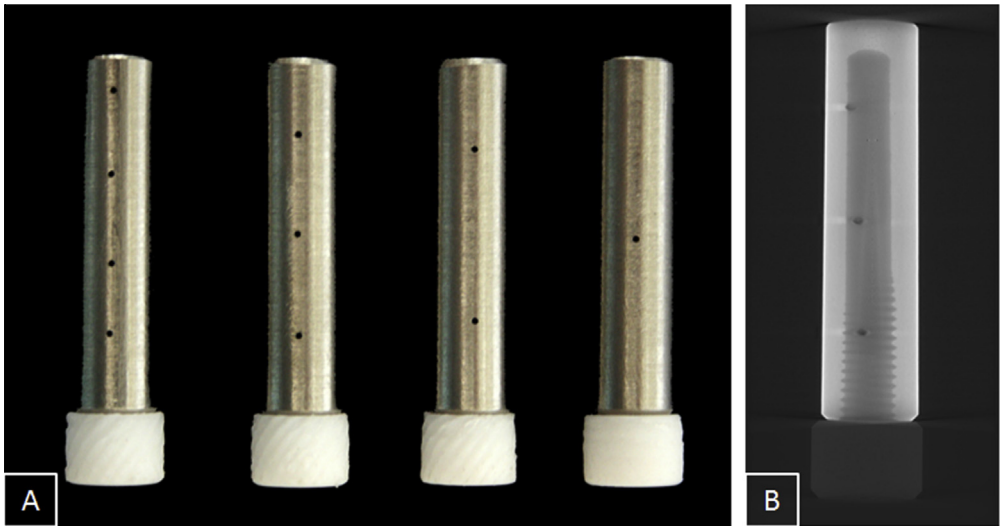

Fig. 1. (A) Lateral image of the four different models of implants tested. Note the equidistant through pinholes. (B) X-ray microtomography of one of the implants (6 pinholes) to show the hollow interior and the screw-in PTFE cap. Note the equidistant through pinholes.

the following molar composition: $142Na^{+}$:5 K^{+}:1.5Mg^{2+}:2.5Ca^{2+}: 148.8Cl^{-}:4.2HCO_3^{-}:1HPO_4^{2-}. The implants were suspended to permit complete contact with the SBF. The linezolid and cefazolin release rates were evaluated in triplicate on independent experiments by measuring the drug concentration in SBF by using 251 nm (linezolid) or 270 nm (cefazolin) UV–vis spectrophotometry at fixed time intervals. Several antibiotic solutions at concentrations of 0, 0.01, 0.025, 0.05, 0.1, 0.2, 0.25, 0.5, 0.75 and 1 mg/ml were used as calibration standards. The means, standard deviations and reproducibility were calculated. The reproducibility can be defined as the closeness of the agreement between independent results obtained with the same method on the test material but under different conditions, in this case, at different experiments. It was measured by using the intra-class correlation coefficient (ICC) for a 95% confidence interval.

2.2. Mechanical studies of the implants

The objective of the mechanical tests is firstly to check the effect of the presence of the pinholes on the global strength of the device, and secondly to compare the load level supported by the device with physiological loads achievable on human bones.

Standardized tests were performed on the implants to analyze the possible influence of the pinholes on the global mechanical strength of the delivery device. Two groups of implant models were examined: the first one without any pinhole and the second one with six pinholes. The geometrical dimensions of all the examined implants were the same, as described in former section, except for the presence of the pinholes. Compression and bending represent the two main load states appearing in long bones as the case of the limbs during the normal activity of the patient. Therefore uniaxial compression and three point bending mechanical tests were performed in a universal hydraulic testing machine Instron 8874. This machine has a resolution of 1 N for a 25 kN load cell and a displacement control test was applied at an axial velocity of 0.1 mm/s.

Implants were subjected to unconfined compression uniaxial tests, positioning the samples between two steel disks and allowing a lateral displacement of the upper end. Five valid tests were carried out for each group, without and with six pinholes. The axial stress-axial strain curves for the groups with and without pinholes were compared.

For the three point bending tests the group of samples with pinholes was divided in two subgroups depending on the relative position of the perforations. Three samples were placed with the holes oriented in the direction of the load while for other three implants the holes were set up in a perpendicular direction. Therefore a total of six valid tests were performed for pinholed implants and other six for intact devices. Displacement control tests at a 0.1 mm/s central point velocity were carried out in an Instron 8874 testing machine with a 25 kN load cell. The tests finished when the total collapse of the samples was reached. Central point force–displacement curves between different groups were analyzed. We tested 6-pinholed samples because they represent the worse situation from a mechanical point of view, because the applied force, and consequently the maximal bending moment, coincides with the central holes of the sample. For the other samples the maximal bending moment does not sit on any of the holes.

2.3. Bacterial challenge studies

S. aureus strain ATCC 6538 was used in all the experiments. Four and six pinholed implants were selected for the bacterial challenge based on the results obtained previously in antibiotic release experiments (see results below).

The classical broth microdilution method [33] was applied to determine the minimal inhibitory concentration (MIC) and the minimal bactericidal concentration (MBC). Previously to the assay, each empty implant was autoclave sterilized, and then filled with lyophilized commercial linezolid or commercial cefazolin powder, according to each experiment. A positive control experiment was included using a pin with no antibiotic. Subsequently they were placed in tubes containing 10 ml of TSB and 10 μl of a stationary culture (10^9 CFU/ml) of the isolate, resulting in a co-culture in exponential growth phase *S. aureus* colonies (10^6 CFU/ml) and maintained at 37 °C. A tube with an empty implant and TSB without bacteria was used as negative control, to check the sterility of the implants.

The bacterial growth on the media was studied at 2, 8, 24 and 48 h. The average number of bacteria was measured by TSA plate count. The experiments were independently done in triplicate and means and standard deviations were calculated.

3. Results

3.1. Kinetic studies of antibiotics release

The release curves of linezolid and cefazolin from the different loaded implants in SBF are shown in Fig. 2. All experiments were performed in triplicate and results are presented as mean ± standard deviation.

For implants with four holes and above, all profiles exhibited a first burst release phase followed by a relatively slower release. The burst release phase is more marked for cefazolin, which has a much larger solubility. The total amount released during this first phase differs for each implant. The release profiles of four, six and eight pinholed implants were markedly faster for cefazolin, especially after the initial burst release. However, similar release profiles are obtained for both cefazolin and linezolid when only two pinholes were used in the implant.

3.2. Mechanical studies of the stainless steel implants

The axial stress–strain curves for the unconfined compression tests are presented in Fig. 3. The initial part of the curves represents the elastic behavior of the implants, exhibiting the same elastic response for both groups. The top end of the samples allowed a lateral displacement, therefore the mechanical failure of the implant would be caused by a combination of plastic behavior and buckling, conducing to some variations of maximal axial stress depending on whether plasticity or buckling prevailed. The maximal stress range obtained for intact implants was 650–850 MPa and for holed samples 750–850 MPa.

Fig. 4 represents the force–displacement curves of the central point of the samples subjected to the three point bending experiment. In this case, the repeatability of the tests is much higher than in the compressive experiments, especially for intact samples. The curves show a first zone of elastic behavior until a load of about 4000 N was reached indicating the plasticity of external points of the central section of the tube. The second zone corresponds to an elastoplastic response with the propagation of plasticity in the points of the central section of the sample. Intact and transversally oriented holed samples present an analogous response, while for samples with the holes oriented in the load direction a different behavior can be observed from a load about 6500 N upward.

3.3. Bacterial challenge studies

The MIC and MBC for the linezolid and cefazolin were separately determined. For linezolid the resulting values were 2 and 16 μg/ml and for cefazolin 1.56 and 12 μg/ml, respectively. These results are in agreement with values previously reported by other authors [34–36].

Both loaded implants showed a strong bactericidal effect after short exposure times (complete bacterial eradication after 24 and 8 h for linezolid and cefazolin-loaded implants, respectively, Fig. 5). The control implant exhibited a linear bacterial growth for linezolid and cefazolin experiments, reaching values around 10^{10} CFU/ml after 48 h of incubation.

After only 2 h of contact, six pinholed cefazolin-loaded implants showed the fastest bactericidal effect presenting 6.6×10^3 CFU/ml whereas four pinholed implants showed 3.6×10^5 CFU/ml and control implant reached 3.3×10^7 CFU/ml, a 4 log increase compared to the six pinholed cefazolin-loaded implant at the same experimental time. For linezolid, the effect seemed to be somewhat slower: four and six pinholed linezolid-loaded implants showed a similar count around 10^5 CFU/ml at 2 h, one order of magnitude lower than the control implant (2.1×10^6 CFU/ml). At 8 h, the control implant reached 9.86×10^8 CFU/ml while 6 pinholed implants

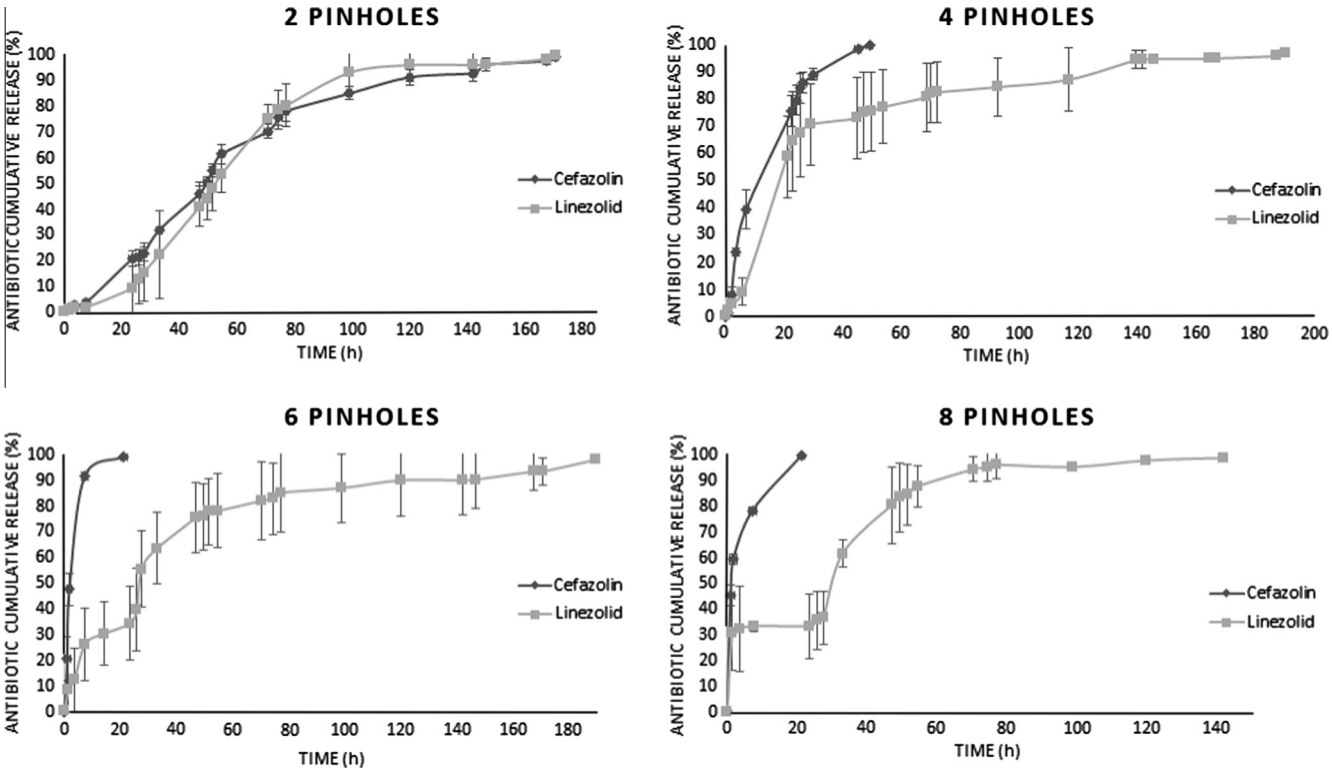

Fig. 2. Linezolid and cefazolin released as a percentage of the antibiotic initially loaded in the different implants immersed in 200 ml of simulated body fluid (SBF). Release profile obtained without replenishing with fresh immersion media. Reproducibility: 2 pinholes (0.95; 0.99); 4 pinholes (0.88; 0.99); 6 pinholes (0.88; 0.98); 8 pinholes (0.84; 0.99) for linezolid and cefazolin, respectively.

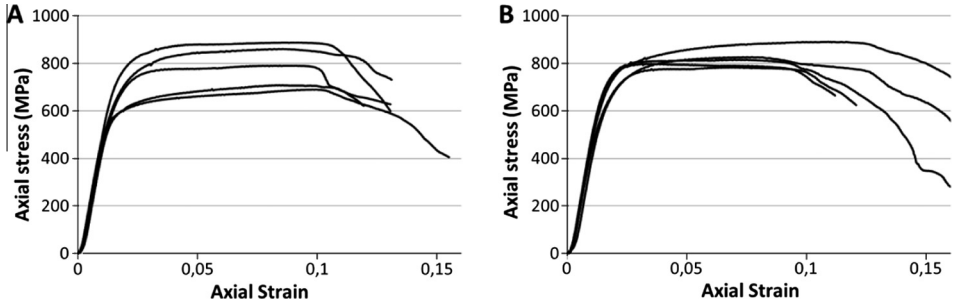

Fig. 3. Axial stress–strain curves for the compression test. (A) No pinholed samples (blank). (B) Six pinholed samples.

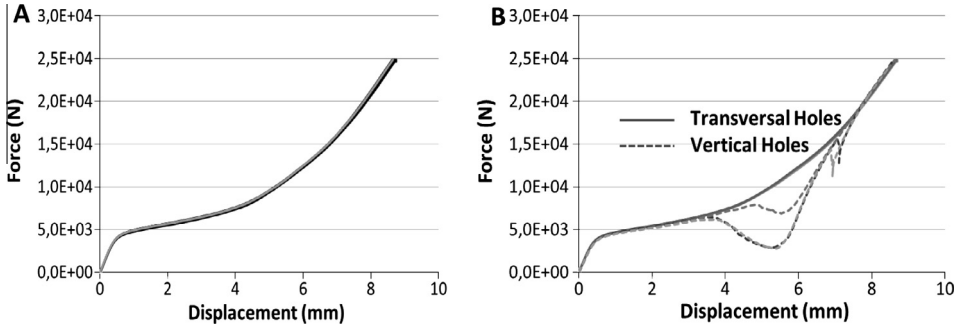

Fig. 4. Central point force–displacement for the three point bending test. (A) No pinholed samples. (B) Six pinholed samples oriented in load and transversal directions.

exhibited 2.1×10^4 CFU/ml (a 4-log reduction in the bacterial count) and four pinholed implants showed 3.46×10^5 CFU/ml. A marked difference in terms of turbidity (caused by bacterial growth) is evident between linezolid and cefazolin eluting implants and the control experiments without any antibiotic at 48 h (Fig. 6).

4. Discussion

Several types of percutaneous and internal metallic devices are used routinely in traumatology and orthopedic surgery to repair, fix or reconstruct damaged bones. The engineering of orthopedic implants that can both prevent infection and facilitate the healing of injured bones could serve as a useful tool in this area by providing the required mechanical strength while offering local antibiotic administration. In addition, with an adequate design of the implant, release at the desired rate would occur without any additional action, avoiding any patient compliance issues.

The 316L stainless steel used on this proof of concept is a widely applied material for biomedical implants. We propose a new design for these bone fixation devices with incorporated antibiotic controlled-release functionality, in which different release profiles can be obtained by changing the type of antibiotic and the number or size of orifices. For the experiments in this work, the antibiotics were loaded as a dry solid. Alternatively, loading the pins with a paste containing a partially pre-dissolved mixture can also be contemplated. In this way, the preventive action can be tailored, according to the patient and medical procedure needs.

The release profiles obtained in this work present a good reproducibility, as shown by the relatively small deviations in triplicate experiments, especially in the case of cefazolin. However, there are marked differences in the observed behavior depending on the number of pinholes (two or more than two pinholes) and on the type of antibiotic. Thus, all implants with four pinholes or more exhibited an initial burst release followed by a slower release phase. However with two pinholes, the process is different, and an induction period appears in the graph, with upward convexity observed for a few hours in the curves of both antibiotics. Also, the release rates are much faster for cefazolin in all implants with four or more pinholes, while they are comparable in implants with only two pinholes. These observations can be explained by considering that the antibiotic release process possibly takes place through the following steps: (i) Surrounding liquid enters the implant; (ii) antibiotic dissolution takes place; (iii) antibiotic is released through the pinholes.

When there is enough exchange area (4 pinholes or more), the surrounding liquid enters the implant rapidly, and dissolution of the antibiotic gives rise to a near-saturated liquid solution close to the inner side of the wall. This creates a gradient for diffusion and release of the antibiotic starts immediately: the antibiotic located closer to the orifices rapidly dissolves, giving rise to the observed burst release for both antibiotics. Since the saturation concentration of cefazolin is one order of magnitude higher than that of linezolid (cefazolin and linezolid solubilities in water at 20 °C are 50 and 3 mg/ml, respectively) [37,38] the driving force for release is much higher, and thus both the magnitude of the burst release stage and the overall release rate through the process are considerably higher for cefazolin, as can be seen for all experiments with 4 or more orifices in Fig. 2. As time progresses, the dissolution front moves inward in the implant and the outside concentration also increases. Both aspects combine to decrease the concentration driving force and as a consequence the system enters in a phase of decreasing antibiotic release rates until all the antibiotic is eventually released (a process that takes 20–40 h for cefazolin, depending on the number of pinholes in the implant and well over 100 h for linezolid). In contrast, when there are only two pinholes, the amount of liquid penetrating the implant is strongly reduced, and capillary processes dominate initially, taking liquid away from the orifices (which gives rise to the observed induction period), and slowing down the release process, as shown in Fig. 2 where comparable rates are obtained for both antibiotics.

A release profile with a burst phase followed by a sustained release of the antibiotic is highly desirable for applications like fracture fixation, where a fast initial release is needed in order to

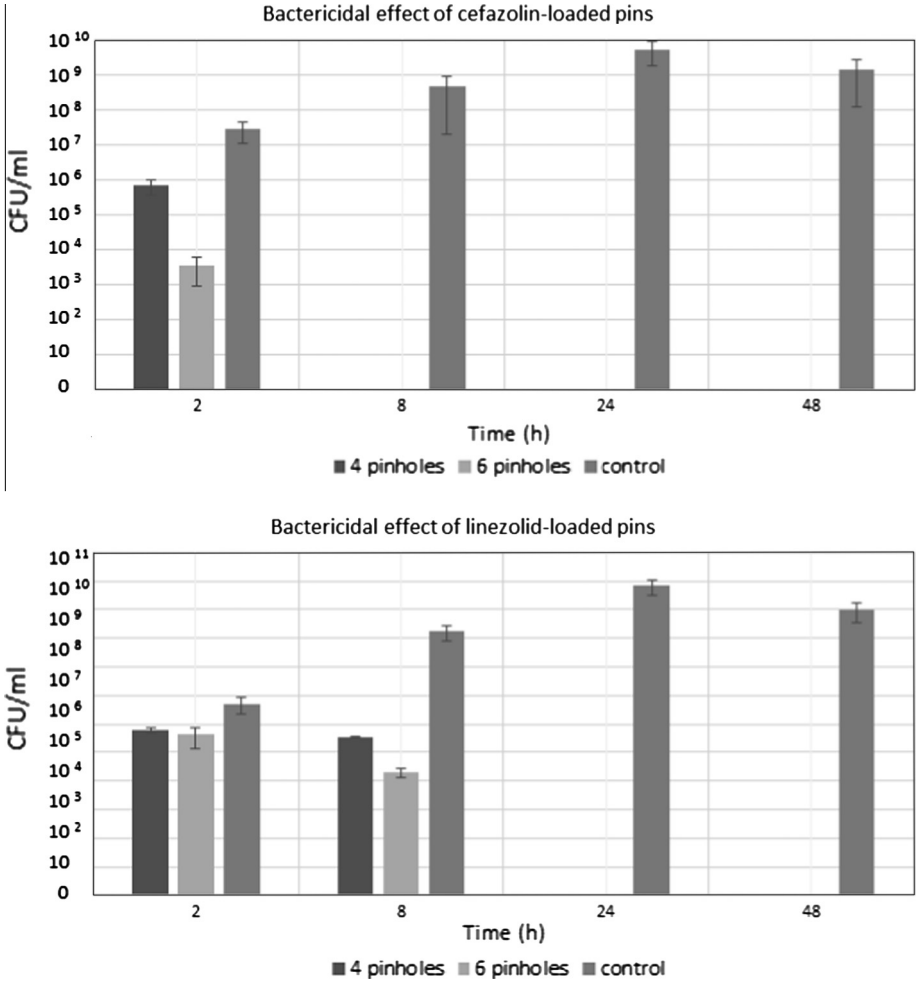

Fig. 5. Kinetics of the bactericidal action for four and six pinholed implants in a 48 h experiment.

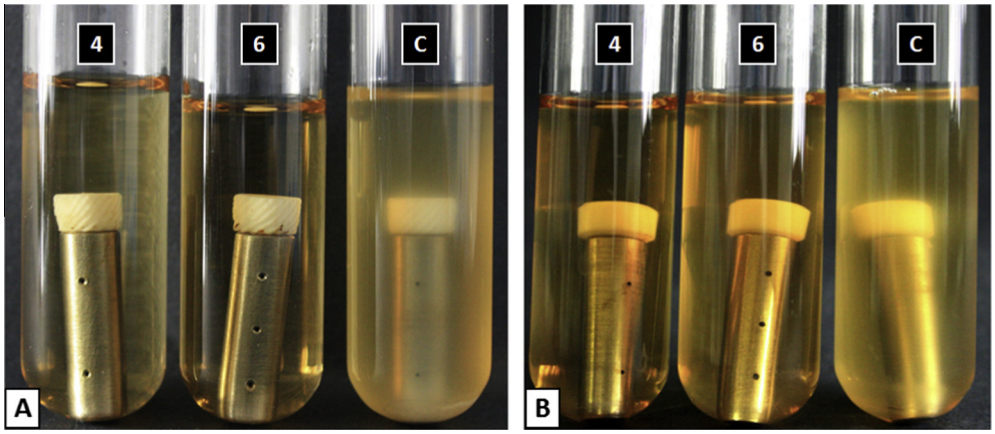

Fig. 6. Digital photograph of four and six pinholed implants containing cefazolin (A) and linezolid (B) and without antibiotics (C) after 24 h culturing with *S. aureus*. Note the marked difference in the turbidity of the media.

prevent infection and eradicate the bacteria in the implant area before they adhere and create a biofilm; this is important because the biofilm formed protects the bacteria from the immune system and hinders penetration of antibiotics [39]. The process of biofilm formation is generally thought to be a two-step model. First, bacteria rapidly adhere to the biomaterial surface by means of hydrophobic and electrostatic interactions. Then the bacteria proliferate and accumulate to form multilayered cell clusters on the surface through molecular and cellular interactions, producing the biofilm [40]. The prevention of the initial adhesion of bacteria to an implant surface is the most important step to avoid biofilm formation. Our results indicate that it is desirable having at least four orifices in the implant (possibly six, if a higher initial flux is required), to ensure a sufficient influx of liquid and fast initial antibiotic release. It is important to point out that no leftover drugs were observed inside the hollow interior after the drug diffusion

tests. This is of the utmost importance to avoid any potential bacterial resistance to the selected antibiotic.

After the surrounding biological fluid has entered the implant and dissolved part of the packed antibiotic, two parameters control the release rate: the total area available for release, which is given by the number of pinholes (and their size, although this aspect has not been investigated in this work), and the solubility of the antibiotic, which gives the maximum concentration attainable in the inner fluid. A higher water solubility and reduced particle size of the cefazolin (<100 μm) compared to linezolid (<300 μm) (see Supplementary information) favor a faster drug release. A higher porosity was expected for the linezolid-based packed beds, due to its larger particle size (in packed beds the size of the interparticle spaces is usually similar to the particle size). However, it is reasonable to postulate that drug solubility plays a controlling role rather than interparticle diffusion limitations.

Mechanical tests were performed to check the effect of the presence of the pinholes on the strength of the device and to compare the load level supported by the device. It can be concluded that the presence of the six holes with the characteristics described does not modify the compressive response of the implant under the loads tested. This level of maximum stress borne by the devices is much higher that the ultimate compressive strength reported for human cortical bone 170 MPa [41]. The three point bending experiment showed that intact and transversally oriented holed samples present an analogous response, while for samples with the holes oriented in the load direction a different behavior can be observed from a load about 6500 N upward. The reason for such load reduction is that the central orifice coincides with the section just above the applied load, reducing the resistant inertia moment and contributing to a stress concentration around the hole. Nevertheless the maximum bearing load is still well above the maximum physiological load supported over a limb, 2.5 times body weight [42]. Therefore neither transversal nor vertical oriented holes are expected to have an impact on the flexural strength of the device under conceivable application scenarios.

Our results indicate that, for both antibiotics tested, an excellent bactericidal action is possible when using drug eluting implants with a sufficient number of orifices. Thus, after only 2 h of contact, cefazolin-loaded implants with 6 pinholes achieved a 4-log reduction in bacterial count. With linezolid the 4-log reduction was achieved after 8 h, but antibiotic release was extended for a much longer period of time. At 2 h cefazolin implants had released approximately 7% and 45% of their load when using four and six pinholes, respectively. This compares with linezolid-loaded implants that after 8 h had released approximately 4% and 10% of their load when using four and six pinholes, respectively. There was a complete bactericidal effect at 24 h and 8 h for linezolid and cefazolin-loaded implants, respectively. This is related not only to the faster release rate of cefazolin due to its higher solubility but also to the fact that the commercial linezolid used contains other components on its pharmaceutical formulation in addition to the antibiotic.

5. Conclusions

Despite the range of prophylactic methods available, bacterial infection remains a major problem in orthopedic procedures. In this context, on-site delivery of antibiotics offers a powerful alternative to fight implant colonization by bacteria in the initial period after intervention. In the absence of a more detailed assessment, the combination of a fast initial delivery followed by prolonged release at a lower rate from a local antibiotic-eluting device appears as a suitable release profile for both traumatology and orthopedic surgery.

As a proof-of-concept we have presented a simple device that allows localized delivery of therapeutic compounds. We have shown that release profiles can be adjusted by selecting the number of release orifices and the type of antibiotic and its solubility. With the number of perforations used in this work, an excellent bactericidal action can be obtained. The release rates can be tailored to match the patient's needs without compromising the mechanical properties of the implant.

This work presents the device concept and preliminary *in vitro* results that show how the release profile can be tailored. Its clinical application would involve re-designing some of the implants currently in use as partially hollow, drug eluting structures. *In vivo* studies are necessary to corroborate the efficacy of the system when facing a more complex scenario with other factors such as body fluid dynamics, clearance and inflammation involved in the healing processes.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejpb.2015.08.007.

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