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Hot melt poly-ε-caprolactone/poloxamine implantable matrices for sustained delivery of ciprofloxacin ☆

Ana M. Puga [a], Ana Rey-Rico [a], Beatriz Magariños [b], Carmen Alvarez-Lorenzo [a], Angel Concheiro [a,*]

[a] Departamento de Farmacia y Tecnología Farmacéutica, Universidad de Santiago de Compostela, 15782-Santiago de Compostela, Spain
[b] Departamento de Microbiología, Universidad de Santiago de Compostela, 15782-Santiago de Compostela, Spain

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ABSTRACT

It has been suggested that prevention and treatment of osteomyelitis could be achieved through local drug delivery using implantable devices, which provide therapeutic levels at the infection site with minimum side-effects. Physical blends of polycaprolactone (PCL) and poloxamine (Tetronic®) were prepared by applying a solvent-free hot melting approach to obtain cytocompatible implants with a tunable bioerosion rate, ciprofloxacin release profile and osteoconductive features. Differential scanning calorimetry and X-ray analysis indicate that the hydrophilic poloxamine varieties T908, T1107, and T1307 are miscible with PCL, while the hydrophobic block copolymer T1301 is immiscible. Incorporation of the block copolymer at weight ratios ranging from 25 to 75 wt.% led to matrices with viscoelastic parameters in the range of those of fresh cortical bone. Once immersed in buffer the matrices underwent a similar weight loss in the first week to the content of poloxamine, followed by a slower erosion rate due to PCL. The initial rapid erosion and the increase in porosity partially explain the observed burst of ciprofloxacin release, which is more intense in the PCL:T1301 formulation due to drug/T1301 repulsion due to polarity. The matrices sustained ciprofloxacin release for several months (<50% released after 3 months) and showed in vitro efficacy against *Staphylococcus aureus*, eradicating the bacteria in less than 48 h. PCL:poloxamine was cytocompatible with osteoblasts and the matrices prepared with low proportions of T908 were also compatible with mesenchymal stem cell differentiation to osteoblasts. The influence of the nature and proportion of temperature-responsive poloxamine on the performance of PCL implantable systems was determined.

1. Introduction

Osteomyelitis is caused by microorganisms that enter bone structures by spreading from the bloodstream or surrounding tissues or by direct contamination during trauma or surgery [1]. Prolonged infection may cause major defects, which require bone grafting or other reconstruction approaches [2]. Current treatment protocols for chronic osteomyelitis combine both surgical debridement of dead bone and prolonged parenteral or oral antimicrobial therapy [2–5]. The efficiency of systemic antimicrobial therapy is limited by poor drug accumulation in bone tissue, an impaired local immune response, changes in bacterial growth rate, biofilm formation and intracellular location of the pathogens [3,4]. Thus systemic treatment should be continued for at least 6 weeks, which causes important collateral effects and makes patient compliance difficult [5]. The development of implantable devices able to provide high levels of antimicrobial agents for a prolonged time at the infection site and with minimized side-effects may improve the efficacy/safety ratio of current therapeutic strategies [6,7].

Both non-biodegradable and biodegradable/bioeliminable materials have been tested as components of depots or implants for the local delivery of antimicrobial agents [8]. Biodegradable/bioeliminable systems can fill the dead space, acting as scaffolds that guide tissue repair and do not require removal after drug release, since they erode as the treatment progresses and the infection regresses [8–12]. Poly-ε-caprolactone (PCL) is relatively cheap and some drug delivery devices fabricated with PCL have already obtained FDA and EMA approval and exhibit suitable rheological and viscoelastic properties for use as implants [13,14]. However, PCL is not widely used clinically yet, mainly because it bioerodes at a slower rate than other aliphatic polyesters [13,15]. Currently available technologies enable the tuning of PCL degradation and drug release rate to fit specific requirements, by forming co-polymers or physical blends with suitable agents [16–19]. Blends with biocompatible polymers are preferable to new co-polymers, since preparation is cheaper and safety is more predictable. Nevertheless, work in this field is still limited [20].

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* Corresponding author. Tel.: +34 981563100x14886; fax: +34 981547148.
E-mail address: angel.concheiro@usc.es (A. Concheiro).

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