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Melt-spun bioactive sutures containing nanohybrids for local delivery of anti-inflammatory drugs

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ABSTRACT

In this work, a novel concept is introduced in drug-eluting fibres to ensure a good control of drug delivery features and wide applicability to different bioactive compounds. Composite bioactive sutures based on fibre grade poly(ε-caprolactone) (PCL) and loaded with the anti-inflammatory drug Diclofenac (Dic) or a Dic nanohybrid where the drug is intercalated in a synthetic hydrotalcite (Mg/Al hydroxycarbonate) (HT–Dic) were developed. Fibres were prepared by melt-spinning at different PCL/HT–Dic/Dic ratios and analysed in terms of morphology, mechanical properties and drug release features. Results emphasized that tensile properties of fibres are clearly affected by Dic or HT–Dic addition, while the presence of knots has limited influence on the mechanical behaviour of the sutures. Release of Dic strongly depends on how Dic is loaded in the fibre (as free or nanohybrid) whereas the combination of free Dic and HT–Dic can allow a further tuning of release profile. In vivo experiments show a reduction of inflammatory responses associated with Dic-loaded fibers. Thus, a proof of principle is provided for a novel class of bioactive sutures integrating advanced controlled-release technologies.

1. Introduction

Sutures are biomedical devices of natural or synthetic origin used to held together tissues that have been separated due to surgery or traumatic injury. Despite the presence of different devices for wound closure (staples, tapes and glues) available on the market, sutures are the most widely diffused in the medical practice and have a market of around 1.3 billion dollars a year [1]. Since a suture should fulfil a number of requirements, unfortunately, no ideal product is available and the surgeon generally operates a selection on the basis of availability and familiarity [2,3]. Nevertheless, an appropriate suture should take into account aspects such as mechanical properties, resorption rate, risk of infection, and inflammatory reactions that may occur during wound healing process. Over the years, new suture materials have been developed to better respond to particular surgical needs. Recently, the research has switched toward a novel concept of medicated suture that includes a bioactive compound which can be released in a defined time frame and help tissue repair.

Research in this area, although being very attractive, has led to very few products successfully entering the market [4–6]. The first commercial antimicrobial suture, a Polyglactin 910 suture loaded with triclosan, a broad-spectrum antibacterial agent (Vicryl Plus®), was approved for clinical uses by the US Food and Drug Administration (US FDA) since 2002 [7]. The basic concept in these sutures consists in coating a preformed polymeric filament with a second biodegradable polymer layer embedding triclosan with the aim to create a zone of inhibition to the spread of bacteria and to exert a preventive action against the possible infection of the surgical site [8]. Nowadays antimicrobial sutures are successfully used in a number of surgical procedures [7, 9–13] with a reduction of wound site infection and consequent cost saving [14]. For all these reasons this treatment strategy was found to be very promising and sutures coated with other drugs such as antithrombotic, analgesics, antineoplastic and antiproliferative agents are under investigation [15].

Recently Lee et al. [16] have proposed a new method to obtain medicated suture where a commercial suture is covered with a polymeric sheet loaded with a pain relief drug. These sutures have been proven

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to have suitable mechanical properties and a drug release only for 6 days. Nevertheless, control of drug release rate is a critical factor to design a bioactive suture in view of an optimized biological effect. For this reason, more suitable strategies are needed to attain both efficient control over drug release rate and adequate mechanical properties. As an alternative to coated fibres, electrospun aligned fibres have been developed where different active agents are dispersed in a polymer to give a matrix-like structure [17–20]. Unfortunately, fibres show weak mechanical properties and electrospinning is difficult to scale-up, making these systems difficult to be applied.

A promising alternative is represented by melt-spinning technology. In this case, a polymer melt is forced through a spinneret capillary to obtain fibres with properties strongly related to the applied drawing extent. The application of this process, even if scalable up to industrial level, is limited in the biomedical field where the usual thermolability of bioactive molecules as drugs and/or the relatively poor elongational properties of biocompatible polymer melts, further worsened by incorporation of additives, may prevent a satisfactory drawing of fibres compromising their ultimate mechanical properties.

Among the strategies useful to control drug release from a polymer matrix, the inclusion of lamellar structures opens new opportunities to develop smart systems. Recently, magnesium and aluminium hydroxycarbonates referred to as hydrotalcite-like compounds (HT) intercalating bioactive molecules have been proposed [21–24]. These systems consist of a layer of inorganic clays which, under specific conditions, self-organize to form a bilayer. In particular Mg/Al LDHs, where some Mg(II) cations are isomorphously replaced by Al(III) cations, generate positive charges balanced by the presence of counteranions located in the interlamellar region. The possibility of replacing these anions by simple ion-exchange procedures makes LDHs a unique class of layered solids to be used as hosts of drugs bearing a negative charge. HTs have already been proven to be biocompatible and some of them are already used in clinical practice as antiacids because of their antipepsin activity [24]. In specific conditions, HT can intercalate different anions or biologically active molecules such as anionic non-steroidal anti-inflammatory drugs (NSAID) [25], antibiotics [26], up to around 50% by weight and form organic–inorganic nanohybrids. Depending on drug features (solubility, molecular weight, affinity to HT), fast dissolution or sustained release of the drug can be accomplished as a consequence of a de-intercalation process [27,28]. Furthermore, a body of interest is growing on the development of novel composites based on inorganic layered materials and organic polymers. Recent studies report on the possibility to introduce organically-modified HT in different polymers as fillers opening a new way to integration of bioactive HT in polymeric films, membranes or fibres with different potential applications in industrial and biomedical field [29–31]. In this context, on the basis of an European patent owned by some participants to this research [32], Sammartino et al. [31] incorporated nanohybrids containing the NSAID Diclofenac (Dic) into poly(ε-caprolactone) (PCL) films and demonstrated effective control of drug release as compared to free drug directly dispersed into the polymer.

Prompted by these considerations, in this paper we offer a proof of principle on the possibility to obtain an anti-inflammatory sustained-release biodegradable suture through the incorporation of a free drug and/or a drug-HT nanohybrid in a thermoplastic polymer. To this purpose a Dic-HT nanohybrid was incorporated in a fibre of poly(ε-caprolactone) (Fig. 1). The fibre was produced by melt spinning and characterized in terms of morphology, size, mechanical properties, drug release and in vivo performance.

2. Materials and methods

2.1. Materials

A nanohybrid containing synthetic hydrotalcite and Diclofenac (HT–Dic, $[Mg_2Al(OH)_6](C_{14}H_{10}Cl_2NO_2) * 2H_2O$, Mg/Al ratio 1.8, distance between layers = 23.6 Å, moisture 7.0%, Diclofenac loading = 59.6%) was obtained from Prolabin & Tefarm (Italy). Diclofenac sodium (Dic) was purchased from Farmalabor (Italy). Poly(ε-caprolactone), PCL, used for this study (CAPA® 6800) was from Perstorp Corporation (UK). HPLC-grade tetrahydrofuran (THF), acetonitrile and methanol, analysis-grade acetone and dichloromethane were from Carlo Erba (Italy). Synthetic hydrotalcite (HT, $Mg_6Al_2(CO_3)(OH_{16}) * 4H_2O$), sodium chloride, potassium chloride, HPLC-grade trifluoroacetic acid (TFA), sodium phosphate dibasic and potassium phosphate monobasic (HPLC grade) were obtained from Sigma-Aldrich (USA). Distilled filtered (0.22 μm) water was employed.

2.2. Fibre production

Fibres were prepared through extrusion, drawing and subsequent cold drawing to the final diameter of approximately 300 μm. Prior to the extrusion process, the components were separately sieved to obtain a fine powder (97% of the powder passed through a #140 sieve with a mesh size of 106 μm according to Ph. Eur. 7th edition). The mean diameter and size distribution of powders were determined by laser light scattering (Coulter LS 100Q, USA). Particle size is expressed as volume mean diameter (μm) ± SD of values collected from three different batches. For Zeta potential measurements, HT–Dic was dispersed in water and analysed on a Zetasizer Nano Z (Malvern Instruments, UK).

The base materials were mixed in a HAAKE twin screw extruder using a screw speed of 20 rpm and applying a temperature profile going from 60 °C, at feed zone, to 100 °C at the die. The filament was cooled in stagnant air (at 23 °C) and collected with a take-up speed of 4 m/min. The as-spun fibres (with a diameter of about 900 μm) were drawn at 50 °C using a Conditioning Unit (DSM Xplore, The Netherland) to the final diameter of about 300 μm (corresponding to a draw ratio of 9).

Different compositions of the fibres, reported in Table 1, were selected in order to investigate i) the effect of Dic intercalated in HT (Dic–HT) as compared to free Dic (PCL/HT–Dic vs. PCL/Dic); ii) the influence of HT in fibres containing free Dic (PCL/HT/Dic vs. PCL/Dic) and iii) the

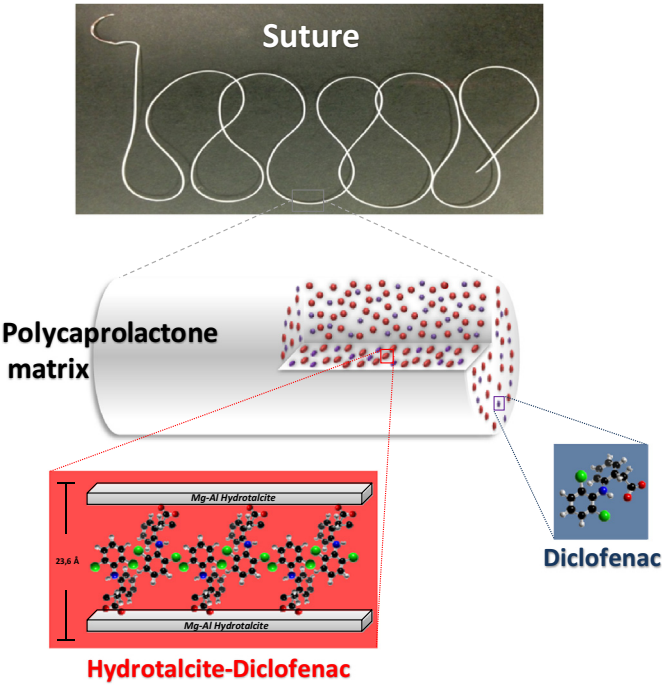

Fig. 1. The concept of anti-inflammatory fibres developed in the study.