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Visceral mesh modified with cyclodextrin for the local sustained delivery of ropivacaine

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ABSTRACT

The aim of the study was to develop a polyester visceral implant modified with a cyclodextrin polymer for the local and prolonged delivery of ropivacaine to reduce post operatory pain. Therefore, we applied a coating of an inguinal mesh with a crosslinked polymer of hydroxypropyl-β-cyclodextrin (HPβCD) whose specific host–guest complex forming properties were expected to improve the adsorption capacity of the implant toward anesthetic, and then to release it within a sustained period.

The modification reaction of the textile with cyclodextrin was explored through the study of the influence of the pad/dry/cure process parameters and the resulting implant (PET–CD) was characterized by solid state NMR and SEM. Besides, the inclusion complex between ropivacaine and CD was studied by NMR and capillary electrophoresis in PBS medium. Finally, ropivacaine sorption test showed that a maximum of 30 mg/g of ropivacaine could be adsorbed on the functionalized samples. In dynamic batch tests in PBS at pH 7.4, the release could be observed up to 6 h. The cytocompatibility of the PET–CD loaded with ropivacaine was also studied and reached 65% cell vitality after 6 days.

1. Introduction

Hernia curing is one of the most practiced acts in visceral surgery in France (John and Patrick, 2008) and more than a million plates were implanted each year in the world. A hernia is a protrusion of viscera through an abnormal opening. In first intention, in some cases, one may reduce this protrusion by holding back the organs inside the abdominal wall using trusses, surgical belts of bindings. If the hernia is not reduced, a strangulation of the viscera of the hernia sac at the level of the collar can appear and lead to necrosis and pain for the patient. To avoid these dramatic complications, hernia is now systematically treated surgically.

The use of prosthetic textiles in the cure of abdominal hernia has known a considerable growth with the advent of laparoscopic techniques and the low recurrence rates (Bouillot et al., 2004). Polyethylene terephthalate (PET) and polypropylene (PP) are common choices of materials for the knitting or weaving intraperitoneal implants. Though, despite the well-known surgical act, complications such as adherences and pain may occur and delay healing and patient's return to normal activity (McGrath et al., 2004). In addition, post-operative pain in the first few days has been recently linked to the appearance of chronic pain (Kehlet et al., 2006), occurring several months after the intervention resulting in morbidity that may require an additional curing act. Such consequences can be prevented by common prophylactic treatment consisting of local injection of morphine derivatives or continued instillation of local anesthetics after implantation (Mentes and Bagci, 2009). Nevertheless, many protocols of postoperative analgesia by direct infiltration in the operated site or continuous instillation of local anesthetics have been proposed without reaching a satisfactory compromise between the process

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and an effective relief (Beaussier and Aissou, 2009; Pélissier et al., 2006). The expected sustained analgesic effect cannot be obtained, due to the fast elimination of the drug from the operated site through corporal fluids (Kfoury et al., 2011).

Then, one approach consists of using drug delivery systems, able to prolong analgesic drug release directly into the targeted site (Pelissier, 2005, US 2006/0034887; Shikanov et al., 2007). For example, Pelissier et al. developed bioadsorbable supports based on a polycaprolactone/polylactic-co-glycolic acid matrix containing bupivacaine or ropivacaine (Pelissier, 2005, US 2006/0034887). After implantation, a burst effect was first observed and the slow degradation of the matrix led to the release of the active principle. Shikanov et al. studied systems based on bupivacaine loaded poly(sebacic-co-ricinoleic) directly injected onto surgical site (Shikanov et al., 2007). *In vitro* tests showed a drug release up to 7 days, whereas the *in vivo* efficiency on mice (Hargreave test) was achieved up to 30 h after injection without any cytotoxicity. Other drug carriers such as microparticles, nanoparticles or liposomes are also widely described in the literature (de Araujo et al., 2008; Görner et al., 1999; Jug et al., 2010; Le Corre et al., 2002; Maestrelli et al., 2010; Sivakumaran et al., 2011; Yu et al., 1998). Among these systems, the use of local analgesic/cyclodextrin complexes looks promising. Cyclodextrins are torus shape cyclic oligosaccharides forming inclusion complexes with numerous organic compounds. It has been demonstrated that thanks to the formation of these inclusion complexes and to their slow dissociation associated to the reciprocal host-guest affinity, the efficient duration of active principles was improved and that their intrinsic systemic toxicity was decreased (de Araujo et al., 2008; Jug et al., 2010).

Another pathway is the modification of textile fibers into local analgesic delivery systems (Kenawy et al., 2009). For example, Kenawy et al. prepared nonwoven textiles based on polycaprolactone/polyurethane containing an anti-inflammatory drug. The drug was incorporated before the electrospinning process. In this study, the degradation of polycaprolactone led to a slow release of the drug after 14 days. However, several parameters such as the use of chloroform or the cost of the process limit the application of these implants. Our group developed a polypropylene (PP) artificial abdominal wall implant for the prolonged release of ciprofloxacin (CFX). This sustained release effect was obtained after functionalization of the textile mesh with citric acid and cyclodextrin. The CD-finished textile showed an increased sorption capacity and a lower release rate of CFX and microbiological assays confirmed this result, with greater sustained antibacterial activity of the CD treated textile (Laurent et al., 2011).

In this context, our strategy consists of preparing a visceral implant functionalized by drug delivery systems directly on its surface, targeting a unique intervention, a slow anesthetic release and an *in situ* activity. Based on the fact that CDs are capable of forming inclusion complexes with amino-amide anaesthetic agents (Jug et al., 2010), we chose to combine ropivacaine and cyclodextrins on a commercial visceral mesh. To this purpose, a polyester inguinal mesh has been functionalized by a polymer of hydroxypropyl-β-cyclodextrin (HPβCD) crosslinked with citric acid (CTR) *via* a pad/dry/cure textile finishing process developed in our laboratory (Martel et al., 2002a,b,b; Weltrowski et al., 1999, EP1157156). The key parameters (time, temperature) have been studied in order to determine the optimal functionalization degree. The modified implants have been characterized by microscopy and NMR to prove the presence of the cyclodextrin coating. Prior to any drug immobilization, we studied the interactions in solution between ropivacaine and cyclodextrin by NMR and affinity capillary electrophoresis. Finally, drug sorption and release have been investigated and the cytocompatibility of functionalized visceral implants with or without analgesic was proved.

2. Materials and methods

2.1. Materials

Polyester (polyethylene terephthalate, PET fibers, Biomesh A1®) plates were manufactured and kindly donated by Cousin Biotech (Wervicq-Sud, France). Hydroxypropyl-β-cyclodextrin (HPβCD, Kleptose® HPB, MS = 0.62, M = 1387 g/mol) was purchased from Roquette Frères (Lestrem, France). Citric acid (CTR), sodium dihydrogen hypophosphite ($NaH_2PO_4{\cdot}xH_2O$) and ropivacaine (M = 274 g/mol) were Aldrich chemicals (Saint Quentin Fallavier, France). Ropivacaine hydrochloride solution (Naropin® 2 mg/mL (20 mL) and Ropivacaine KABI 10 mg/mL (10 mL) were respectively purchased from AstraZeneca (London, United Kingdom) and Kabi (Bad Homburg, Germany)).

Water soluble polyCTR-HPβCD used in the NMR and capillary electrophoresis experiments for the study of the inclusion complexation with ropivacaine was synthesized according to a method previously reported (Martel et al., 2002a; Weltrowski et al., 2003). The molecular weight was in the range of 50 kg/mol determined by SEC equipped with LLS detector using water as solvent and the HPβCD content in the polymer was 50 wt% determined by ^{1}H NMR.

2.2. Methods

2.2.1. Polyester meshes functionalization

The textile finishing process with CDs was based on a pad/dry/cure textile finishing process previously reported (Martel et al., 2002a,b,b; Weltrowski et al., 1999, EP1157156). The PET meshes were impregnated and roll-squeezed in an aqueous solution containing HPβCD, catalyst (NaH_2PO_2) and CTR, whose composition is reported as 8/1/10, where 8, 1 and 10 are related to the weight in gram unit of HPβCD, catalyst and CTR, respectively, dissolved in 100 mL of pure water. The fixation reaction occurred in a thermo-fixation oven (Minithermo®, Roaches, UK). A kinetic study was carried out at temperatures comprised between 130 and 160 °C and during 5–60 min. After this treatment, all meshes were thoroughly washed in Soxhlet extractor with distilled water (Aquadem, Veolia) in order to remove the unreacted products. The degree of functionalization (DF, unit wt%) was reported as the weight gain of the samples by using the following equation:

$$\mathrm{DF} = \frac{m_f - m_i}{m_i} \times 100$$

where m_i and m_f correspond respectively to the sample weight before and after treatment, measured with a precision balance ($\pm 4 \times 10^{-4}$ g). Before weighing, all samples were preliminarily dried at 104 °C for 1 h and cooled down to room temperature in a desiccator during 30 min. The DF corresponds to the weight increase of the textiles due to CD polymer fixation upon finishing treatment under the standard conditions.

2.2.2. SEM

The SEM investigations were carried out on a Hitachi S-4700 SEM FEG (Field Emission Gun) operating with an acceleration voltage of 5–25 kV, after carbon metallization.

2.2.3. NMR studies

The functionalization of PET with HPβCD was characterized by solid state CPMAS ^{13}C NMR (400 MHz, BRUKER). The spectrometer was equipped with a 4 mm CPMAS probe. The samples were spun at 10 kHz speed.

The complexation between HPβCD or polyCTR-HPβCD and ropivacain was observed by ^{1}H NMR (400 MHz, BRUKER). Aliquots