International Journal of Pharmaceutics 513 (2016) 483–495

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical nanotechnology

Triclosan loaded electrospun nanofibers based on a cyclodextrin polymer and chitosan polyelectrolyte complex

Safa Ouerghemmi[a], Stéphanie Degoutin[a], Nicolas Tabary[a], Frédéric Cazaux[a], Mickaël Maton[b], Valérie Gaucher[a], Ludovic Janus[a], Christel Neut[c], Feng Chai[b], Nicolas Blanchemain[b], Pr. Bernard Martel[a,*]

[a] CNRS 8207, UMET, University Lille 1, 59655 Villeneuve d'Ascq, France
[b] INSERM U1008, CHU Lille, Controlled Drug Delivery Systems and Biomaterials, 59000 Lille, France
[c] INSERM U995 LIRIC, Laboratory of Bacteriology, College of Pharmacy, 59000 Lille, France

ARTICLE INFO

Article history:
Received 15 July 2016
Received in revised form 19 September 2016
Accepted 20 September 2016
Available online 21 September 2016

Chemical compounds studied in this article:
Chitosan (PubChem CID: 71853)
Triclosan (PubChem CID: 5564)
Polyethylene oxide (PubChem SID: 160698351)
Cycloheptaamylose, beta-cyclodextrin (PubChem CID: 101136808)

Keywords:
Electrospinning
Cyclodextrin polymer
Chitosan
Polyelectrolyte complex
Nanofibers
Triclosan
Antibacterial activity
Controlled release

ABSTRACT

This work focuses on the relevance of antibacterial nanofibers based on a polyelectrolyte complex formed between positively charged chitosan (CHT) and an anionic hydroxypropyl betacyclodextrin (CD)-citric acid polymer (PCD) complexing triclosan (TCL). The study of PCD/TCL inclusion complex and its release in dynamic conditions, a cytocompatibility study, and finally the antibacterial activity assessment were studied. The fibers were obtained by electrospinning a solution containing chitosan mixed with PCD/TCL inclusion complex. CHT/TCL and CHT-CD/TCL were also prepared as control samples. The TCL loaded nanofibers were analyzed by Scanning Electron Microscopy (SEM), Fourier Transformed Infrared spectroscopy (FTIR) and X-Ray Diffraction (XRD). Nanofibers stability and swelling behavior in aqueous medium were pH and CHT:PCD weight ratio dependent. Such results confirmed that CHT and PCD interacted through ionic interactions, forming a polyelectrolyte complex. A high PCD content in addition to a thermal post treatment at 90 °C were necessary to reach a nanofibers stability during 15 days in soft acidic conditions, at pH = 5.5. In dynamic conditions (USP IV system), a prolonged release of TCL with a reduced burst effect was observed on CHT-PCD polyelectrolyte complex based fibers compared to CHT-CD nanofibers. These results were confirmed by a microbiology study showing prolonged antibacterial activity of the nanofibers against *Escherichia coli* and *Staphylococcus aureus*. Such results could be explained by the fact that the stability of the polyelectrolyte CHT-PCD complex in the nanofibers matrix prevented the diffusion of the PCD/triclosan inclusion complex in the supernatant, on the contrary of the similar system including cyclodextrin in its monomeric form.

1. Introduction

Nanocarriers such as nanoparticles, nanofibers, liposomes, micelles have gained a widespread attention for their great potential to control drug release (Xu et al., 2007). Indeed, controlled drug delivery systems aim to improve the therapeutic efficacy by releasing the drug at the appropriate rate and over a necessary healing period. Nanofibrous materials have been arising as a promising candidates for controlled drug delivery systems (Gainza et al., 2015; Sill and von Recum, 2008; Weng and Xie, 2015). Electrospinning is the most used technique to produce polymeric nanofibers. It is a cost-effective, scalable and useful technique. It affords the possibility to use a rich variety of polymers including hydrophilic, hydrophobic, synthetic or natural ones (Choi et al., 2013; Aguilar et al., 2015; Lin et al., 2013; Kai et al., 2014; Huang et al., 2003; Xu et al., 2013a; Jiang et al., 2005), of different molecular weights and at different concentrations. These polymers not only provide mechanical properties for the drug carrier but may also present a bioactivity such as antibacterial and antithrombotic properties. Furthermore, a wide range of drugs can be combined to electrospun networks such as antibacterial or anticancer agents (Brewster et al., 2004; Jiang et al., 2014; Paaver et al., 2015). Thus, the drug can be associated to nanofibers by dissolution in the polymer solution, by covalent conjugation or inclusion complexation, by coating or surface grafting, or else more

* Correspondence to: Université Lille 1, Unité Matériaux et Transformations, Bâtiment C6, Bureau 119, 59655 Villeneuve d'Ascq, France.
E-mail address: bernard.martel@univ-lille1.fr (B. Martel).

http://dx.doi.org/10.1016/j.ijpharm.2016.09.060
0378-5173/

by coaxial electrospinning (Ardeshirzadeh et al., 2015; Aytac et al., 2015, 2014; Jiang et al., 2014; Llorens et al., 2015; Meinel et al., 2012; Son et al., 2014). Depending on the association mode, the release will be rapid or sustained with an important or reduced *burst* effect. Several researches are focused on the factors that impact the release profile. Among these factors, the drug solubility, state and loading rate in nanofibers (Natu et al., 2010) in addition to the variation of the electrospinning process parameters which could highly modify the drug release profile (Brewster et al., 2004; Lin et al., 2013; Paaver et al., 2015; Pillay et al., 2013). In fact, each parameter has an influence on the fiber diameter size, the porosity, the fiber orientation, the swelling degree and the degradation rate of the fibers.

In this purpose, cyclodextrins (CD) and cyclodextrin polymers appear to be good candidates for controlled drug release systems (Challa et al., 2005; Otero-Espinar et al., 2010; Uekama et al., 1998). Thanks to their hydrophobic cavities, cyclodextrins could form reversible inclusion complexes with a large variety of drugs, notably the hydrophobic ones, which lead to improve the solubility and the bioavailability. Moreover, cyclodextrin can be easily modified to form ionic derivatives. The literature abounds with studies that report the use of cyclodextrin polymers as drug carrier (El Fagui and Amiel, 2012; Gidwani and Vyas, 2014; Junthip et al., 2015; Martel et al., 2005; Oliveira et al., 2015; Xin et al., 2010; Zhang et al., 2010). An anionic crosslinked water-soluble cyclodextrin polymer, obtained from a reaction between a CD and a polycarboxylic acid, was largely studied in our group as a drug carrier (Bakkour et al., 2006; Danel et al., 2013). Up to our knowledge, the electrospinning of cyclodextrin polymer in all its forms is little studied in the literature, particularly for biomedical applications. Some studies have been reported for other types of applications using a blend of CD and poly(acrylic acid) wherein the polymerization takes place in situ after a heat treatment of the nanofibers (Aytac et al., 2016; Zhao et al., 2015). Nevertheless, one study reported by M.F. Oliveira and coworkers has investigated the synthesis of cyclodextrin polymer via the polycondensation of βCD and epichlorohydrin and the electrospinning of a cyclodextrin polymer in blend with Poly(methyl methacrylate) (PMMA) for the release of a hydrophilic drug (Oliveira et al., 2015). They studied the *in vitro* release of propranolol hydrochloride from bulk and coaxial nanofibers and its potential for drug delivery application. In contrast, several studies have reported the elaboration of nanofibers composed of native cyclodextrins and cyclodextrin derivatives for drug loading (Aytac et al., 2015, 2014). Though, the drug release from these materials occurs not only by the diffusion of the drug out of the nanofibrous matrix, but also by the diffusion of the CD-drug inclusion complex itself. This phenomenon can be attributed to the solubilization of the complex once the nanofibers are immersed and swelled in contact with aqueous media. In the present study, the strategy was to prevent the inclusion complex

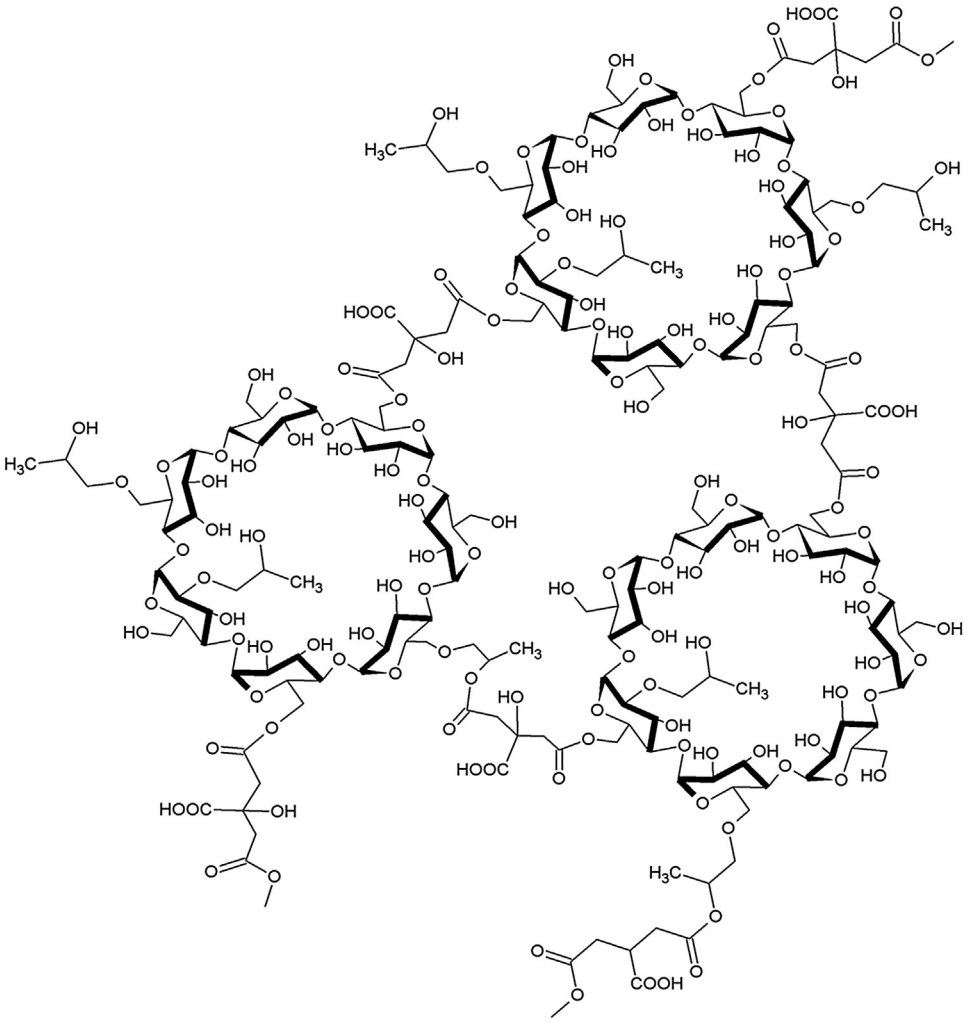

Fig. 1. Detailed chemical structure of polyHPβCD.