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On the degradation properties of electrospun fibers based on PLLA: The effect of a drug model modification

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ABSTRACT

In this work, the features of electrospun fibers based on poly(L-lactide) (PLLA) containing drug model molecules, which were modified as to render them more dispersible in the polymer matrix and potentially capable of tuning the PLLA degradation, were investigated. Indeed, the above compounds, constituted by a pyrene terminal group attached to a short chain of poly(D-lactide) (Pyr-D) or PLLA (Pyr-L), were synthesized by employing 1-pyremethanol (Pyr-OH), a widely applied hydrophobic model drug, as the initiator of the ring opening polymerization (ROP) of L- or D-lactide. ^{1}H NMR measurements allowed to calculate the oligomer molecular masses, which resulted to be in satisfactory agreement with the theoretical value. With the aim at verifying the influence of the synthesized compounds on the material final properties, electrospun fibers characterized by different compositions were prepared, that is fibers based on neat PLLA, PLLA with Pyr-OH, PLLA with Pyr-L, PLLA with Pyr-D and PLLA with Pyr-OH and Pyr-D, by adding an amounts of the various additives in order to obtain the same pyrene content. The morphological characterization, accomplished by means of FE-SEM, evidenced that the addition of the above compounds did not significantly influence the morphology of the fibers. Conversely, the fluorescent microscopy measurements demonstrated a different dispersion of the pyrene-based additives in the various samples, namely an aggregation of Pyr-OH and a homogeneous distribution of Pyr-L as well as Pyr-D. The fiber thermal properties were investigated by DSC measurements. In general, the annealing treatment, accomplished at 80 °C for 4 h, turned out to increase the system crystallinity. Furthermore, as confirmed also by X-ray diffraction analysis, the fibers containing the Pyr-D additive were found to be characterized by a partial stereocomplexation resulting from the combination of the PDLA chain of Pyr-D with those of PLLA matrix. Enzymatic degradation tests, conducted on both annealed and non-annealed samples, indicated that the thermal treatment as well as the addition of Pyr-D significantly decreased the rate of the fiber degradation. As such, the release of pyrene, followed in time by UV measurements, was related to the system degradation and stereocomplexation, it being much slower in the fibers containing Pyr-D.

1. Introduction

Drug delivery technology has benefited from the exploitation of polymers mainly because the resulting systems can be characterized by a tunable release of both hydrophilic and hydrophobic drugs [1–3]. The pharmacologic active molecules are generally released from polymer systems via one of the following mechanism: i) diffusion through water-filled pores or through the polymer matrix [4,5], ii) osmotic pumping [6] and iii) degradation of the matrix [7–9]. Concerning the latter mechanism, the control of the polymer decomposition is of crucial importance, since it regulates also the drug release. Indeed, in the drug delivery applications the exploitation of degradable polymers, such as polylactic acid (PLA), the object of the present work, has become prominent due to their biocompatibility and degradability properties, as they can break down inside the body, producing nontoxic components [10]. In general, the degradation of these polymers can occur as a surface [7,8] or a bulk process [8,9]. In the surface degradation, the polymer matrix is progressively removed from the surface, while in bulk decomposition no significant change occurs in the physical size of the polymer until it is almost fully degraded but the fraction of

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polymer remaining in the carrier decrease over time. In particular, PLA decomposition, which is mainly induced by hydrolysis and catalyzed by enzymes, depends on the intrinsic features of the polymer, such as the chemical composition (homo and co-polymers), physical properties (molecular weight, crystallinity, etc.) and tacticity [11–13]. Concerning the latter aspect, it is worth underling that the combination of poly(L-lactide) (PLLA) and poly(D-lactide) (PDLA), producing stereocomplexed systems [14], leads to materials characterized by a higher hydrolysis resistance compared with that of mere PLLA and PDLA [15–19]. Indeed, Tsuji et al., who widely studied the decomposition of stereocomplexed systems [15–18], found that the activation energy for the degradation of stereocomplex crystallites (97.3 kJ mol^{-1}) was significantly higher than that reported for the α-form the PLLA crystallites (75.2 kJ mol^{-1}), thus indicating the higher hydrolysis resistance of stereocomplex as compared to PLLA crystallites. Moreover, in an in vivo study on the biocompatibility of PLLA and stereocomplexed nanofibers by subcutaneous implantation in rats, Ishii et al. also observed that stereocomplexed nanofibers showed slower degradation than PLLA [19].

Generally, the hydrolysis of PLA has been studied using proteinase K, an endopeptidase enzyme responsible for the hydrolysis of peptides amides in keratin and other proteins. Indeed, the use of degradation solutions composed by water and enzyme buffer may provide insight into some aspects of the degradation process of certain biomaterials since enzymes and other reactive species are expected to be present in the in vivo environment [20]. It is worth underling that proteinase K was found to preferentially degraded L-lactyl units as opposed to D-lactyl ones [21]. Concerning the decomposition of stereocomplex systems by enzymatic hydrolysis, Lee et al. [21] found that in the presence of proteinase K, the hydrolysis rate of the mixture PLLA/PDLA was much slower than that of the single component. This phenomenon was connected to the strong interactions between PLLA and PDLA chains, which prevents the penetration of water or enzyme into the bulk.

Another important issue, which is necessary to face in the development of the polymer/drug systems, is related to the dispersion of the drug which needs to be homogenously distributed throughout the material. In particular, in the case of electrospun fibers, a polymer architecture used in this work and highly applied in the biomedical field, one of the most important factor, affecting the drug distribution and consequently its sustained release, was found to be the drug-polymer compatibility [22]. Indeed, the latter parameter refers to the physical interactions between drug molecules and polymer chains, which will influence the drug distribution in the matrix.

On this basis, it is of great interest the developing of novel polymer/drug formulations characterized by a uniform dispersion of the pharmacological active molecule and a modulating degradation of the polymer matrix, which leads to a controllable release of the drug. In the designing our system, made up of PLLA electrospun fibers and an ad-hoc modified drug model, we considered both these issues, namely the drug dispersibility and the polymer decomposition. Indeed, the modification of the drug was aimed at making it compatible with the polymer matrix and rendering it potentially capable of influencing PLLA structuring and hence its degradability. As drug model, a pyrene molecule, namely 1-pyremethanol (Pyr-OH), which is generally used as model of hydrophobic drugs, it being also a fluorescent probe, was used and modified. The synthesized molecules, made up of a pyrene end group and PLLA or PDLA short chains (Pyr-L and Pyr-D), which were prepared via ROP of L- or D-lactide, using Pyr-OH as initiator, should guarantee a high dispersibility, thanks to the chains of equal nature to those of the polymer matrix. Moreover, in the case of the exploitation of Pyr-D, the polymer and the drug model decomposition and release, might be related to the system structuration, namely to the formation of a stereocomplex system by the combination of the PDLA-type chains of Pyr-D with PLLA. In order to evidence the effect of the chemical modification of the drug on the material final properties, different formulations were prepared. As shown in Fig. 1, the properties of the neat PLLA fibers were compared with those of the mats containing the drug model (Pyr-OH), the synthesized modified drug molecules (Pyr-D and Pyr-L) and the mixture of Pyr-OH and Pyr-D. The fibers were characterized in terms of morphology, thermal propertied, hydrolytic decomposition and the drug model release from the prepared systems were monitored in the time.

2. Experimental section

2.1. Materials

D-lactide (D-la) and L-lactide (L-la) (purity >98%) were kindly supplied by Corbion Purac (The Netherlands). Before

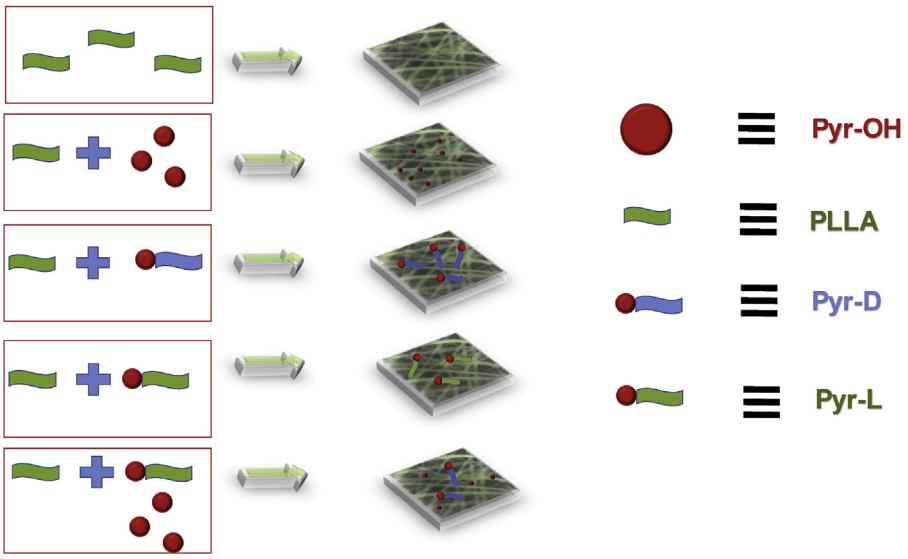

Fig. 1. Scheme of the prepared formulation based on PLLA electrospun fibers.