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Polyphosphazenes with amino acid citronellol ester side groups for biomedical applications

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ABSTRACT

In order for a material to be considered a potential candidate as a scaffolding substrate, it should be biodegradable to non-toxic products, and possess similar physical characteristics to those of the living tissue being replaced. Previous work centered on the direct linkage of citronellol, an anti-inflammatory molecule, to a polyphosphazene backbone. Moreover, the hydrolysis rate in that study was tuned by incorporating alanine ethyl ester co-substituent units thereby decreasing the amount of citronellol in the final polymer. By contrast, in this work citronellol was used as an ester unit linked to the carboxylic acid moiety of the amino acids glycine, alanine, valine, and phenylalanine that were in turn linked to the polymer backbone through the amino functionality. This method allowed the hydrolysis rate to be controlled via the steric hindrance generated by the amino acid ester while still providing two crosslinkable sites per repeat unit from the citronellol units. A hydrolysis study of the uncrosslinked polymers at physiological temperature showed between a 19.8% and 28.8% mass loss and between a 80.4% and 98.9% molecular weight decline after 12 weeks. The double bond in the citronellol structure also allowed polymer crosslinking by UV radiation to further control the polymer properties.

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1. Introduction

Current solutions for repair of the millions of ligament and tendon injuries occurring annually primarily utilize autografts and allografts. These are non-ideal [1]. The shortcomings include limited living tissue availability, increased healing times, and the risk of infection [2]. Among the alternative solutions currently under investigation, the field of tissue engineering has emerged as a prominent candidate [3–6]. This approach uses a biodegradable polymer scaffold, seeded with cells and signaling molecules, for implantation in place of the damaged ligament or tendon [7,8]. As the polymer degrades slowly the incorporated signaling molecules induce the body to slowly rebuild the damaged tissue [9,10]. A number of natural and synthetic polymers have been investigated for this application as they meet some of the necessary scaffold characteristics such as biocompatibility or biodegradability [11–14]. Thus, silk and collagen have been studied extensively; however, their use is limited by batch to batch inconsistencies and uncontrollable enzymatic degradation in the body [15]. One of the most commonly studied synthetic polymers is poly(lactic acid), due to its good mechanical properties and FDA approval, but its hydrolysis into acidic monomers and oligomers can cause tissue necrosis at the implant site and this has limited its viability [16]. Another key requirement for a scaffold material is that it must have similar mechanical properties to those of the parent tissue [17]. An elastomeric polymer would be an ideal matrix material for tendons and ligaments because the scaffold would be subjected to numerous loading and unloading cycles [18]. Attempts are also being made to improve the performance of natural and

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synthetic fibers using different scaffold fabrication techniques such as knitting or braiding [19–22].

In the current work we have explored a new method for polymer synthesis to favor the properties required for ligament and tendon tissue engineering applications. For this, we used polyphosphazenes due to their high degree of synthetic tunability [23,24]. These macromolecules possess a backbone of alternating phosphorus and nitrogen atoms with two organic groups attached to each phosphorus atom [25]. They are synthesized from a reactive macromolecular intermediate, poly(dichlorophosphazene), $(NPCl_2)_n$, by replacement of the chlorine atoms by reactions with various alkoxide or amino nucleophiles [26]. The properties of the resultant polymers are controlled by both the properties of the skeleton and those of the organic side groups [27,28]. The goal of this work was to utilize side groups that would facilitate degradation of the polymers to non-toxic products, while also favoring the generation of elastomeric characteristics. Previous research in our program demonstrated that amino acid ethyl ester polyphosphazenes hydrolyze into the non-toxic by-products, specifically amino acid, ethanol, phosphates, and ammonia, fulfilling the first requirement for a bioerodible biocompatible material [29,30]. The flexibility of the polyphosphazene backbone makes it possible to design polymers with low glass transition temperatures (as low as −100 °C) [31,32]. The combination of flexible polymers with crosslinkable side groups together with the additional ability of the system to break down slowly should provide access to polymers that meet the requirements for ligament or tendon replacement or repair [33].

To accomplish this objective we used citronellol units connected to the polymer backbone through an amino acid ester linker unit. This methodology is related to previous work wherein an amino acid was used as the attachment site for a desired molecule onto the polyphosphazene backbone [34–36]. The structures in this report maintained a high constant citronellol density along the polymer chain, but allowed the steric hindrance of different amino acid units to control the hydrolytic degradation rate. This differs from earlier work in which citronellol was attached directly to a polyphosphazene backbone, a situation in which the hydrolysis rate could only be tuned by incorporating various ratios of a second type of skeletal-linked side group, an option that decreased the amount of citronellol that could be incorporated into the final polymer [37]. Thus, in this work we explore the use of citronellol as a carboxylic acid ester moiety for the amino acids glycine, alanine, valine, and phenylalanine, themselves serving as a bridge between the phosphazene backbone and the citronellol.

2. Results and discussion

2.1. Synthesis of amino acid citronellol ester side groups

Every amino acid used for chlorine replacement in phosphazenes requires the carboxylic acid moiety to be protected to avoid side reactions [38,39]. Traditionally this was accomplished by using the ethyl ester of the amino acid [40]. Other previous work has utilized longer chain alcohols to esterify the carboxylic acid units in an attempt to determine the effect of the steric bulk of the alcohol on the hydrolysis rate and physical properties of the final polymers [29,30,41]. However, in this present work citronellol was used to esterify the amino acid in order to provide the necessary unsaturated functionality which can act as a crosslink site. In addition, citronellol has antimicrobial and anti-inflammatory properties, which may be beneficial for a tissue engineering application [42–45]. The syntheses for all side groups followed a similar protocol (Scheme 1). These yielded the side group unit as its HCl salt [41]. The HCl salt was then converted to the neutral form utilizing triethylamine as a base. Triethylamine also serves to capture the HCl released when the amino functionality reacts with the P—Cl bond of the polymer. The insolubility of the TEA–HCl complex provides a driving force for both reactions. This is important because free HCl in the reaction medium could protonate the polymer backbone and cause skeletal cleavage.

2.2. Synthesis of the cyclic trimer as a model system *(6)*

The feasibility of using a citronellol amino acid ester as a side group for poly(dichlorophosphazene) reactions was monitored using the small molecule cyclic trimeric hexachlorocyclotriphosphazene (**5**) as a reaction model. This was carried out to identify any synthetic challenges that might arise when attempting chlorine replacement on the high polymer [46]. To this end, the largest side group in question, L-phenylalanine citronellol ester, was chosen for the model synthesis. The synthesis is shown in Scheme 2. This reaction progressed without complication and the product was identified by mass spectrometry and ^{31}P NMR analysis. The ease of this procedure supported the idea that these side groups could also be linked to the high polymer backbone.

2.3. Synthesis and characterization of polymers *8–11*

All the polymer substitution reactions were performed in a similar manner, as shown in Scheme 3. The reactive intermediate, poly(dichlorophosphazene) (**7**), was generated by the ring-opening polymerization of hexachlorocyclotriphosphazene (**5**) in a sealed system at 250 °C. This polymer was then treated with nucleophiles **1**–**4** for chlorine replacement as discussed. Triethylamine (TEA) was added to the reaction mixture as an acid scavenger to sequester the hydrogen chloride (HCl) generated during the substitution reaction as an insoluble complex. However, the TEA–HCl complex is slightly soluble in the reaction mixture and is a potential cause of backbone cleavage [47]. Thus, the substitution reaction was monitored by ^{31}P NMR spectroscopy and was promptly terminated and the polymer purified before skeletal cleavage became serious. Specifically, the disappearance of the poly(dichlorophosphazene) ^{31}P peak at $\delta = -17$ ppm and the appearance of a new peak at $\delta = 0$ ppm, represented a polyphosphazene unit substituted with two amino acid ester side groups, and this was used to determine when the substitution reaction was complete. The characterization data for the resultant amino acid citronellol ester

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