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Adaptable poly(ethylene glycol) microspheres capable of mixed-mode degradation

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ABSTRACT

A simple, degradable poly(ethylene glycol) (PEG) microsphere system formed from a water-in-water emulsion process is presented. Microsphere network degradation and erosion were controlled by adjusting the number of hydrolytically labile sites, by varying the PEG molecular weight, and by adjusting the emulsion conditions. Microsphere size was also controllable by adjusting the polymer formulation. Furthermore, it is demonstrated that alternative degradation and erosion mechanisms, such as proteolytic degradation, can be incorporated into PEG microspheres, resulting in mixed-mode degradation. Owing to the adaptability of this approach, it may serve as an attractive option for emerging tissue engineering, drug delivery and gene delivery applications.

1. Introduction

Hydrogels have been used in many different applications involving gene delivery, drug delivery and tissue engineering because of their biocompatibility, high water content and tunable network properties [1,2]. Poly(ethylene glycol) (PEG) hydrogels have been commonly used in these applications, in part because of their biological inertness and the relative ease of functionalization of the PEG polymer [3]. While hydrogels fabricated solely from PEG are typically stable in physiological conditions, PEG copolymers can be designed to be labile over time, resulting in biodegradable hydrogels [3–5]. Biodegradable PEG hydrogels have been fabricated using a variety of chemistries, and have been engineered to degrade via simple hydrolytic or enzyme-catalyzed mechanisms [3–16].

PEG hydrogels are often used in the form of PEG microspheres. In most applications of microspheres made from polymeric materials, two key parameters are their degradability and size [1,17–19]. Microsphere size has been shown to influence cellular interactions with the microspheres [1,18] and the release rate of incorporated soluble molecules by changing the surface area to volume ratio [1,20–21]. Additionally, microsphere size has been identified as a key parameter when microspheres are incorporated into stem cell aggregates (e.g., embryoid bodies) [19] or assembled to form tissue engineering scaffolds [22–25]. Microsphere degradation and erosion also influence the rate of release of incorporated soluble molecules [1], and have been identified as important parameters during in vivo drug delivery applications. Non-erodible microspheres can cause long-term toxicity and are eventually difficult to remove [17]. Collectively, these previous works demonstrate a need for adaptable approaches to create biodegradable microspheres with controllable size and degradation rate. There is also a need for microspheres that degrade not only by simple hydrolysis, but also by biologically induced mechanisms (e.g., protease activity) to match microsphere degradation rates with biological events such as wound healing [26]. Many methods of synthesizing degradable PEG microspheres have been reported previously, such as the use of PLGA/PEG blends [27] and copolymers [28,29]. However, some current methods use complex synthesis steps, thus limiting the use of these microspheres in the broader scientific community.

This study presents a simpler, adaptable approach to fabricating PEG microspheres with controllable size, degradation time-frames and mixed-mode degradability. PEG-diacrylate (PEGDA) polymer chains were first reacted with dithiol molecules via a Michael-type addition reaction to form polymer chains with hydrolytically labile ester linkages proximal to thioether bonds (Fig. 1A). A water-in-water emulsion process was then used to synthesize PEG microspheres without the use of organic solvents [30,31]. Degradation and erosion of the resulting hydrogel networks were controlled pri-

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