Synthesis and Characterization of Biodegradable Networks Providing Saturated-Solution Prolonged Delivery

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ABSTRACT: Numerous peptide drugs require continuous and local delivery to obtain optimum therapeutic effect. Herein, we describe the incorporation of a model peptide drug, vitamin B12, as well as goserelin acetate, in biodegradable elastomer cylinders through photo-cross-linking. The elastomer was prepared from acrylated *star*-poly(ε-caprolactone-*co*-D,L-lactide). Release was manipulated through the incorporation of poly(ethylene glycol) diacrylate (PEGD) into the network at concentrations up to 30% (w/w). The PEGD in the network caused rapid swelling that remained constant throughout the release period. The degree of swelling was low, ranging from 10 to 45% (w/w), and increasing as the PEGD content increased. Release proceeded with a minimal initial burst, and extended periods of nearly constant release, ranging from approximately 5 to 70% mass fraction released, were obtained. The release rate was independent of particle size and increased as the cylinder diameter decreased, as the amount of PEGD increased, as the molecular weight of PEGD increased, and as the agent loading increased. Moreover, goserelin acetate, which has a comparable diffusivity but greater aqueous solubility, was released at a greater rate than vitamin B12. This release behavior is explained as a balance between agent dissolution in the swollen polymer matrix and diffusion through the polymer matrix bulk. J Pharm Sci 97:860–874, 2008

Keywords: photo-cross-linking; biodegradable elastomer; poly(ethylene glycol) diacrylate; peptide delivery

INTRODUCTION

Many peptide and protein drugs, such as cytokines for example, are effective at very low concentrations, have very short biological half-lives, act in a paracrine fashion, require long-term delivery and are rapidly degraded when administered by conventional routes. For these reasons considerable effort has gone into the development of formulations for their prolonged localized delivery, much of which has focused on the use of biodegradable polymers as delivery vehicles.[1–4] In particular, the development of biodegradable microparticle formulations has received considerable attention.[3,4] A less studied biodegradable system is the cylindrical geometry. There are several advantages of a cylindrical system over the microparticulate form. These include simpler manufacturing procedures, facile implant removal if necessary, and consistently higher peptide loading efficiencies.[4] An example of a marketed cylindrical delivery system for peptide delivery is Zoladex, which consists of goserelin acetate distributed throughout a poly(lactide-*co*-glycolide) matrix.[5,6]

Although it has a demonstrated biocompatibility, poly(lactide-*co*-glycolide) is a brittle material at body temperature. Elastomeric polymers as

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drug delivery depots possess potential advantages over the more brittle poly(lactide-*co*-glycolide). These advantages include less tissue irritation at the implant site and, for covalently cross-linked elastomers, maintenance of geometric dimensions during release and degradation.[7] Maintenance of geometry during release is important in obtaining a predictable release rate. Covalently cross-linked elastomers can be prepared using heat induced or photo-irradiation induced reactions. For the entrapment of temperature sensitive drugs such as peptides, a thermal setting elastomer would not be suitable. Photo-cross-linking, on the other hand, can be accomplished very rapidly, with minimal heat generation,[8] which may prevent degradation of the peptide drug to be entrapped.

For drugs that need to be released at low concentrations but within a reasonable time frame, the use of a hydrophobic polymer matrix is a poor choice, as drug release rates are controlled by the interconnectedness of the particles within the matrix.[2,4] In these delivery systems the drug is incorporated as a solid particle dispersed throughout the polymer matrix. The drug is released by dissolution and diffusion of surface resident particles and any particles in contact with these particles. Subsequent release for biodegradable systems then proceeds through the creation of micropores within the device as the polymer begins to hydrolyze. For low drug loadings, only a small fraction of the drug particles are interconnected, and so the majority of the drug is released through the creation of pores by polymer degradation. This generally results in a biphasic release pattern, with release by diffusion occurring first, followed by a lag period wherein little drug is released, then a final period of polymer degradation rate-controlled release.

One means of increasing the amount of drug released in the diffusional period is the inclusion of physiologically innocuous, water-soluble solid excipients in the device.[9–12] These excipients dissolve to generate pores in the device through which the incorporated drug can be released, and may also enhance polymer degradation by increasing water absorption into the device. The inclusion of water-soluble excipients may also eliminate the biphasic release pattern. As an alternative to including excipients, a hydrophilic polymer can be incorporated into the network. The hydrophilic polymer would be more homogeneously distributed throughout the matrix than a solid excipient, and thus could provide more predictable release rates.

We have therefore explored the use of a photo-cross-linkable biodegradable elastomer as a peptide delivery vehicle in a cylindrical device, wherein a hydrophilic polymer was also incorporated into the network. Low molecular weight photo-cross-linkable star copolymers of ε-caprolactone and D,L-lactide were prepared and co-cross-linked with linear poly(ethylene glycol) diacrylate in a suspension of either vitamin B12, as a peptide drug analog, or goserelin acetate. Vitamin B12 was used as a drug analog because it is readily detectable due to its red color and has a molecular weight similar to that of many peptide drugs. Various parameters thought to affect the release rate were examined: the loading of vitamin B12, the poly(ethylene glycol) content, poly(ethylene glycol) molecular weight, cylinder diameter, particle size, and star copolymer molecular weight. The release mechanism was probed by comparing the release of vitamin B12 to that of goserelin acetate. These two molecules have comparable diffusivity, but different solubility, in water.

MATERIALS AND METHODS

D,L-Lactide (99%) was obtained from Purac America Inc. (Lincolnshire, IL) and purified by re-crystallization from hot toluene, while ε-caprolactone was obtained from Alfa Aesar (Ward Hill, MA), dried over CaH_2 (Aldrich, Mississauga, Ontario, Canada) and distilled under vacuum in a nitrogen atmosphere. Other chemicals used were stannous 2-ethylhexanoate, glycerol, acryloyl chloride, triethylamine, 4000 g/mol poly(ethylene glycol) diacrylate (PEGD), 4-dimethylaminopyridine, and 2,2-dimethoxy-2-phenyl-acetophenone, which were all obtained from Aldrich, Canada. Other chemicals used include dichloromethane and ethyl acetate obtained from Fisher, Canada and 24000 g/mol poly(ethylene glycol) diacrylate obtained from Polysciences, Inc. (Warrington, PA).

Polymer Synthesis

The photo-cross-linkable *star*-poly(ε-caprolactone-*co*-D,L-lactide) was prepared as described previously.[13,14] Briefly, 50:50 molar ratio copolymers were prepared of molecular weights of 1250, 2700 and 3900 g/mol by melt ring-opening polymerization of ε-caprolactone and D,L-lactide at 140°C for 24 h initiated by glycerol and catalyzed by