



Photo-crosslinked networks prepared from fumaric acid monoethyl ester-functionalized poly(D,L-lactic acid) oligomers and N-vinyl-2-pyrrolidone for the controlled and sustained release of proteins

Janine Jansen^a, Martijn P. Tibbe^a, George Mihov^b, Jan Feijen^c, Dirk W. Grijpma^{a,d,*}

^a MIRA Institute for Biomedical Technology and Technical Medicine, Department of Biomaterials Science and Technology, Faculty of Science and Technology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands

^b DSM Ahead, P.O. Box 18, 6160 MD Geleen, The Netherlands

^c MIRA Institute for Biomedical Technology and Technical Medicine, Department of Polymer Chemistry and Biomaterials, Faculty of Science and Technology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands

^d W.J. Kolff Institute, Department of Biomedical Engineering, University Medical Center Groningen, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands

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ABSTRACT

Photo-crosslinked networks were prepared from fumaric acid monoethyl ester-functionalized poly(D,L-lactic acid) oligomers and N-vinyl-2-pyrrolidone. Two model proteins, lysozyme and albumin, were incorporated into the network films as solid particles and their release behavior was studied. By varying the NVP content and macromer molecular weight the degradation behavior and protein release profiles of the prepared networks could be tuned. The more hydrophilic and less densely crosslinked networks released albumin and lysozyme at a faster rate. Although active lysozyme was released from the networks over the complete release period, lysozyme release was often incomplete. This was most likely caused by electrostatic and/or hydrophobic interactions between the protein and the degrading polymer network.

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1. Introduction

In the past decade several researchers have investigated the use of photo-crosslinked biodegradable polymer networks for controlled drug delivery applications [1,2]. A major advantage of photo-crosslinking is that a drug can easily be entrapped in a network by dispersing or dissolving it in a macromer solution prior to crosslinking. In this way large amounts of drug can be loaded at high efficiencies. Furthermore, photo-polymerization is rapid and can be accomplished with minimal heat generation, allowing the incorporation of heat-sensitive compounds such as proteins.

Poly(D,L-lactic acid) (PDLLA) is a well-known polymer that has been studied extensively for application in biodegradable drug delivery systems [3]. Networks based on PDLLA can be prepared by photo-initiated crosslinking of functionalized PDLLA oligomers. Besides the frequently used methacrylate derivatives, fumaric acid derivatives are also attractive compounds for endfunctionalization reactions. It can be expected that residual unreacted fumarate

endgroups will not lead to toxicity upon implantation since fumaric acid is a compound naturally found in the body [4]. The relatively low reactivity of fumarate endgroups can be overcome by choosing an appropriate co-monomer for the photo-initiated crosslinking reaction, such as N-vinyl-2-pyrrolidone (NVP) [5].

Many photo-crosslinked polymer networks have been studied as drug delivery systems. These include photo-crosslinked highly swollen hydrogels [6–8] and more hydrophobic networks based on PDLLA, poly(ε-caprolactone), poly(trimethylene carbonate) (PTMC) or co-polymers of these three [9–12]. Drug release profiles can be tuned by varying the crosslink density or by adjusting the hydrophilicity of crosslinked polymer networks. Several authors have used the incorporation of poly(ethylene glycol) (PEG) to increase network hydrophilicity and adjust drug release profiles [13–15]. Increasing the NVP content of networks prepared from fumaric acid derivatives was shown to also increase network hydrophilicity and drug release rates [16–18].

Controlled and sustained release of protein drugs is challenging due to the large size and the relative instability of these molecules. During preparation, storage and release a range of conditions may affect the stability of a protein [19,20]. Important in this respect is the possible presence of residual organic solvents. When incorporating protein drugs in photo-crosslinked polymer networks care

* Corresponding author at: MIRA Institute for Biomedical Technology and Technical Medicine, Department of Biomaterials Science and Technology, Faculty of Science and Technology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands. Tel.: +31 53 4892966; fax: +31 53 4892155.

E-mail address: d.w.grijpma@utwente.nl (D.W. Grijpma).