Controlled Release | Targeted Delivery | Solubility Enhancement

FORMULATION OF POLY(ETHYLENE GLYCOL) HYDROGELS FOR DRUG DELIVERY


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Introduction

Hydrogels are an attractive vehicle for localized administration of pharmaceutical agents such as proteins and small molecules that can be released in a temporally and spatially controlled manner. By maintaining a high local concentration of a drug, hydrogels bypass the need for systemic drug administration and provide a reservoir of the drug to be released slowly over time. Poly(ethylene glycol) (PEG) is a hydrophilic polymer that, when crosslinked and swollen with water, produces a three-dimensional (3D) hydrogel capable of encapsulating drugs and cells. Therefore, PEG hydrogels have been studied extensively as a platform for drug delivery and tissue engineering. PEG hydrogels may be an ideal drug delivery vehicle due to favorable host-material interactions: they are non-toxic, biocompatible, resist biofouling, and are non-biodegradable.[1] The mechanical properties of PEG hydrogels are also well-defined and can be tuned for application, including the drug delivery site and drug diffusion kinetics, by modifying PEG molecular weight and crosslink density.[2] Functionalization of PEG allows for further robust modification of the chemical and mechanical properties of PEG hydrogels. But perhaps the simplest synthetic addition is acrylation, which allows crosslinking via free radical additions (**Figure 1**).

PEG can be end-functionalized with a variety of other groups, including methoxy, hydroxy, maleimide, thiol, and azide moieties, all of which are commercially available in homobifunctional and heterobifunctional forms. The diversity of functional groups allows unique crosslinkers with different crosslinking chemistry, such as Michael-type additions, thiol-ene and Diels-Alder click reactions, enzymatic reactions, and carbonyl additions.[3] These reactions can be triggered with ultraviolet light, changes in pH, temperature, electromagnetic fields, or the addition of other chemical compounds.[4]

PEG-hydrogel Drug Delivery Applications

Drug delivery from a hydrogel involves the diffusion of an encapsulated pharmaceutical agent through the bulk of the gel into the immediate microenvironment surrounding the delivery site. Depending on the porosity, hydrophilicity, and other physicochemical properties of the hydrogel and the drug, the loaded drug can elute slowly over time in a pharmacokinetically controlled manner that prolongs circulation time.[5] Many different agents have been used in PEG-containing hydrogel drug delivery applications, including small molecules,[6] macromolecules,[7] and nano/microparticles.[8–9] Such formulations have been applied to cutaneous, ocular, and cardiac tissue, among others.

Although described as a "bioinert" drug delivery platform, PEG hydrogels can also incorporate bioactive materials, such as extracellular matrix amino acid motifs or macromolecules such as collagen.[10] Incorporation of biological macromolecules facilitates integration into the native tissue environment due to cell-integrin recognition of extracellular matrix components such as laminin, fibronectin, collagen, and hyaluronic acid. This may be important for drug delivery applications where degradation of the hydrogel, and therefore drug release, should be mediated by the host microenvironment. Control of degradation is, therefore, critically dependent on the composition of the hydrogel and the sensitivity of the degradable sequences.

Interpenetrating Networks of PEG and Biological Materials

Due to the poor mechanical stability of biologically derived hydrogels such as collagen, many have incorporated PEG into the polymer matrix to enhance the mechanical strength and longevity *in vivo*. In general, interpenetrating networks (IPNs) consist of a binary system of two polymers that are chosen to better control the physical and biological properties of the hydrogel. Fusion of synthetic and biological materials can be via physical entanglement or covalent crosslinking. Several groups have incorporated hyaluronic acid into degradable PEG hydrogels in an IPN to increase cell proliferation and activity for cartilage, cutaneous, vocal folds and other soft tissue.[11–12] The PEG in these formulations is typically modified with poly(lactic acid) or similar copolymer to facilitate degradation. Another formulation uses chitosan, a natural polysaccharide derived from crustacean shells, often used in wound healing applications.[13]

A robust and versatile IPN platform that consists of cysteine-conjugated gelatin processed from collagen (Gel-PEG-Cys), and PEG-diacrylates

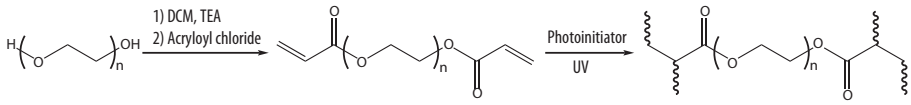

Figure 1. Synthesis of a PEG-diacrylate hydrogel.