

Bioactive Hydrogels



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The first report of the synthesis of composite materials comprising conducting polymers and hydrogels was in 1994 by Wallace et al.¹ Their objective was to enhance the porosity and ion-transport properties of hydrogels for controlled drug

delivery through electrochemically stimulated release of analytes. Since then, the electrochemical and oxidative polymerization of pyrrole, aniline, and thiophene and their derivatives within hydrogel hosts, such as polyacrylamide, poly(acrylic acid), chitosan, and poly(HEMA) have been routinely accomplished for biosensor applications and to achieve voltage-stimulated or controlled release. There have also been several studies conducted on the fabrication of polymer blends of hydrogels, such as poly(methyl methacrylate) (PMMA), poly(vinyl methyl ether) (PVME), poly(4-vinylpyridine),² and poly(2-hydroxyethyl methacrylate) (p(HEMA)), primarily for the construction of artificial muscles.^{3,4} With hydrogels, high degrees of hydration (ca. 90 %) could be reversibly achieved along with biocompatibility, good refractive index matching with water, and relative ease of molecular engineering. In general, the conducting polymer component of these composites retains their electroactive properties.

Brahim et al.⁵ have fabricated bioactive polypyrrole-p(HEMA) composites to function as sensing membranes for clinically important amperometric biosensors. A monomer cocktail containing, among other components, the relevant methacrylate monomers, pyrrole or aniline, and photoinitiator was spin-cast onto microfabricated electrodes and first irradiated by UV to effect polymerization of the hydrogel components. This was immediately followed by potentiostatic electropolymerization of the pyrrole/aniline monomer in a phosphate-buffered potassium chloride solution saturated with further monomer. Amperometric enzyme biosensors for the detection of glucose, cholesterol, and galactose were demonstrated, each possessing extensive linear dynamic response ranges, high sensitivities, and prolonged storage stabilities.⁶

Of particular recent interest is the development of **bioactive** (containing biologically active moieties such as bioactive peptides, growth factors, enzymes and the like) and **biosmart** (responsive to biologically derived external stimuli) electroconductive hydrogels for implant biocompatibility. A novel polymer composite material consisting of a water-dispersed complex of polypyrrole doped with polystyrenesulfonate and embedded in polyacrylamide hydrogel was prepared and evaluated as a matrix for enzyme immobilization.⁷ The enzyme glucose oxidase was physically entrapped in the polymer by inclusion in the aqueous phase during emulsion polymerization. The resulting bioactive microparticles (3.5–7.0 μm diameter) were cast onto platinum electrodes and the polymer-modified electrodes used as amperometric glucose biosensors. This configuration displayed rapid response times and efficient screening of interferents.

For implantable biosensing applications, the synthesis of hydrogel composite polymers consisting of cross-linked p(HEMA) with incorporated polypyrrole and/or polyaniline chains are rendered “bioactive” by the covalent immobilization of oxidoreductase enzymes. Enzymes were first “monomerized” by hetero-bifunctional coupling of the amines of the lysine residues of

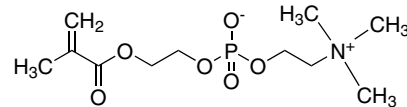


Figure 1. Structure of 2-methacryloyloxyethyl phosphorylcholine

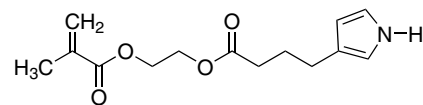


Figure 2. Structure of 2-methacryloyloxyethyl pyrrolylbutyrate

the enzyme (typically 1:2) with acryloyl (polyethylene glycol)₁₁₀ *N*-hydroxy succinamide ester (Acryl-PEG-NHS). This allowed the covalent immobilization of the tethered oxidoreductase enzyme within the hydrogel milieu. To provide for stabilization of the immobilized enzymes, poly(ethylene glycol)₂₀₀ monomethacrylate (PEGMA) was also included in the monomer cocktail at 0.5 mol %. Together these components allowed photolithographically defined, spin-cast membranes formed on microlithographically defined electrodes to recognize and amperometrically respond to the enzyme's substrate and achieve approximately one year of retained enzyme activity (ca. 80%). For implant biocompatibility, the synthesis of the monomer 2-methacryloyloxyethyl phosphorylcholine (MPC) (**Figure 1**) was accomplished by the coupling of HEMA with 2-chloro-2-oxo-1,3,2-dioxaphospholane (COP).⁸ When incorporated into the hydrogels at the level of ca. 5–10 mol %, this monomer conferred nonthrombogenicity, reduced protein adsorption, and supported cell viability. Mimicking the zwitterionic head group of the outer leaflet of cell membranes, phosphatidyl choline, the phosphorylcholine moiety confers the molecular equivalent of “stelt” to the polymer when the biosensor is implanted. When cultured with muscle fibroblasts and endothelial cells, these highly porous hydrogel composites support the migration and mobility of cells within its 3-D network⁹; a property that will render these materials appropriate for the fabrication of nerve electrodes and cellular interfaces as the polymer mimics the biological structures that enable cells to grow.

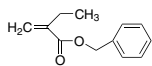
One challenge faced by the use of electroactive polymers as components of hydrogels for mammalian implantation is the potential toxicity. Early work has established polypyrrole as bio-benign. However, to address this issue, bi-functional monomers of pyrrole such as 2-methacryloyloxyethyl pyrrolylbutyrate (MPB) (**Figure 2**) and aniline that may be UV-polymerized, and hence, covalently coupled into the hydrogel network and also oxidatively polymerized with imbibed free pyrrole or aniline monomer to form the electroactive polymer component were developed. In this way, an interpenetrating network of the electroactive polymer is formed within the preformed hydrogels network that serves as the reactor. Studies are ongoing to evaluate the potential cytotoxicity and biocompatibility of these polymers.

References: (1) Small, C. J. et al. *Polymer Gels and Networks* **1997**, *5*, 251. (2) Asberg, P.; Ingana, O. *Biosens. Bioelectron.* **2003**, *19*, 199. (3) Pich, A. et al. *Polymer* **2002**, *43*, 5723. (4) Douglass, P. M, et al. *Soc. Automotive Eng.* **2000**, 1. (5) Brahim, S. et al. *Biosens. Bioelectron.* **2002**, *17*, 53. (6) Brahim, S. et al. *Electroanalysis*. **2002**, *14*(9), 627. (7) Rubio Retama, J. et al. *Biosens. Bioelectron.* **2004**, *20*, 1111. (8) Brahim, S. et al. *Microchimica Acta* **2003**, *143*, 123. (9) Abraham, S et al. *Biomaterials* **2005**, *26*(23), 4767. (10) Abraham, S.; Guiseppi-Elie, A. *Biomaterials* **2006**, submitted for publication.

Monomers for Bioactive Polymers

Benzyl 2-ethyl acrylate, 99% NEW

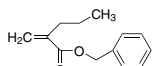
C₁₂H₁₄O₂
MW: 190.24



589136-250MG 250 mg

Benzyl 2-propylacrylate, 99% NEW

C₁₃H₁₆O₂
MW: 204.26



590126-250MG 250 mg

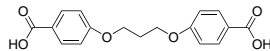
1,6-Bis(p-acetoxycarbonylphenoxy)hexane, 97% NEW

C₂₄H₂₆O₈
MW: 442.46

657174-1G 1 g

1,3-Bis(4-carboxyphenoxy)propane, 97% NEW

C₁₇H₁₆O₆
MW: 316.31
MP: 310 °C(lit.)



655538-5G 5 g

1,6-Bis(p-carboxyphenoxy)hexane, 90% NEW

C₂₀H₂₂O₆
MW: 358.39

655546-5G 5 g

2-Chloro-1,3,2-dioxaphospholane-2-oxide NEW

C₂H₄ClO₃P
MW: 142.48
MP: 12–14 °C (lit.)
BP: 89–91 at 0.8 mm Hg (lit.)



377953-1G 1 g

377953-5G 5 g

2-Ethylacrylic acid, 98% NEW

C₅H₈O₂
MW: 100.12
BP: 176 °C (lit.)



589128-250MG 250 mg

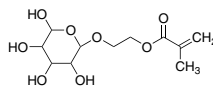
Ethyl 2-propyl acrylate, 99%

C₈H₁₄O₂
MW: 142.2
BP: 141 °C (lit.)

590118-250MG 250 mg

Glycosyloxyethyl methacrylate, 5% (w/v) solution in ethanol NEW

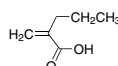
C₁₂H₂₀O₈
MW: 292.28



659576-25ML 25 mL

2-Propylacrylic acid, 99% NEW

C₆H₁₀O₂
114.14
165–188 °C (lit.)



591009-100MG 100 mg

591009-1G 1 g

Pyrrole, 98%

C₄H₅N
MW: 67.09
MP: –23 °C (lit.)
BP: 131 °C (lit.)



131709-25ML 25 mL

131709-100ML 100 mL

131709-500ML 500 mL

2-Vinylpyridine, 97%

C₇H₇N
MW: 105.14
BP: 79–82 °C (29 mm Hg) (lit.)



132292-5ML 5 mL

132292-100ML 100 mL

132292-500ML 500 mL

4-Vinylpyridine, 95%

C₇H₇N
MW: 105.14
BP: 62–65 °C (15 mm Hg) (lit.)



V3204-5ML 5 mL

V3204-100ML 100 mL

V3204-500ML 500 mL

1-Vinyl-2-pyrrolidinone, 99+% NEW

C₆H₉NO
MW: 111.14
BP: 92–95 °C (11 mm Hg) (lit.)



V3409-5G 5 g

V3409-250G 250 g

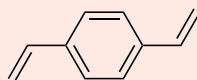
V3409-1KG 1 kg

V3409-18KG 18 kg

Three grades of HEMA (2-hydroxyethyl methacrylate) are available: 97% (128635), 98% (525464), 99+% (477028).

For a comprehensive list of hydrogel hosts such as polyacrylamide, poly(acrylic acid), chitosan and poly(HEMA), as well as functionalized PEGs (linear, 4-arm and 6-arm), visit sigma-aldrich.com/biocomp.

Cross-linkers



DVB, 85% (535583)

Cross-linking is the formation of chemical links between molecular chains to form a three-dimensional network of connected molecules. The strategy of covalent cross-linking is key to the formation of hydrogels. It is also used in several other technologies of commercial and scientific interest to control and enhance the properties of the resulting polymer system or interface, such as thermosets and coatings.

For a complete list of cross-linkers, visit us at sigma-aldrich.com/biocomp and scroll down to cross-linkers.

For questions, product data, or new product suggestions, please contact the Materials Science team at matsci@sial.com.