Anti-tumor Drug Delivery Using Oligo(polyethylene glycol) Hydrogel

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Introduction: Oligo(polyethylene glycol) fumarate (OPF) hydrogels have been shown to be effective in tissue engineering and drug delivery applications. Hydrogels can be injected into the site where treatment is needed and cross-linked *in situ* by ultraviolet light. These characteristics of OPF hydrogels are particularly advantageous in targeting sites of cancerous cells while maintaining a therapeutic dose. Also, side effects of chemotherapy can be minimized with controlled drug delivery. We have previously shown that OPF hydrogel can be used for DNA delivery to normal and cancerous bone cells.[1]

In this study, OPF hydrogels are utilized for controlled delivery of Doxorubicin which is commonly used in treatment of a wide range of cancers. The use of Doxorubicin and its derivatives cause dilated cardiomyopathy and congestive heart failure due to the accumulation of the drug and Dox-induced cardiotoxicity. In this report, we demonstrate that Doxorubicin can be encapsulated within the photo-cross-linked OPF hydrogel and the process of cross-linking has no effect on Doxorubicin bioactivity. We show that encapsulated Doxorubicin can be released in a controlled manner over 9 days and released Doxorubicin preserves its anti-tumor activity.[2]

Methods: OPF was synthesized from purified PEG (initial MW 1k, and 10k) according to a previously published method.[2] OPF macromer (final concentration 33% w/w), photoinitiator Irgacure 2959 (0.05% w/w; Ciba-Specialty Chemicals, Tarrytown, NY), and co-monomer N-vinyl pyrrolidinone (3.3% w/w) were dissolved in deionized water and sterilized using 0.02 µm filter under vacuum (Steriflip®, Millipore, Billerica, MA). [2-(methacryloyloxy) ethyl]-trimethyl ammonium chloride was used for incorporation of the electrical charge to the hydrogel. Hydrogel precursor was placed on glass plates with 2 mm spacer height and polymerized using 365 nm UV light at the intensity of ~8 mW/cm^2 for 30 min. Crosslinked hydrogels were cut into discs of 6 mm diameter with a cork borer and lyophilized overnight. Doxorubicin (100 µM) was encapsulated within the hydrogel by adding to the hydrogel precursor before crosslinking.

MG63 human osteosarcoma cells (25,000 cells/cm^2) were maintained in DMEM/F12 media supplemented with 10% fetal calf serum media. Cells were maintained at 37°C and 5% CO_2. To determine the biological activity of released Doxorubicin, MG63 cells were cultured in 24-well tissue culture plates and transwells containing Doxorubicin-loaded hydrogels submerged in the cell culture media. MTS Cell Proliferation Assay (Promega Corporation, Madison, WI), was used to assess cell survival by metabolic activity after treatment. In order to test release period and its efficiency, after 3 days of treatment new set of plates with cells were exposed to same Dox-loaded hydrogel.

Results: Our results show that continuous death of MG63 osteosarcoma cells was observed in the group treated with hydrogel loaded doxorubicin (Fig.1). Whereas, in control groups (hydrogel without Dox and tissue culture polystyrene; TCPS), the cell growth was not affected and the cells remained viable (Fig.1)..In addition, our data show that swelling ratio of OPF hydrogel changes with the change in molecular weight of PEG in OPF and the charge density of hydrogel (Fig 2). The hydrogel swelling ratio is a function of hydrogel mesh size and affects the release kinetics of anti-tumor drugs. Further investigation is required to optimize the release kinetic of Doxorubicin from OPF hydrogels.

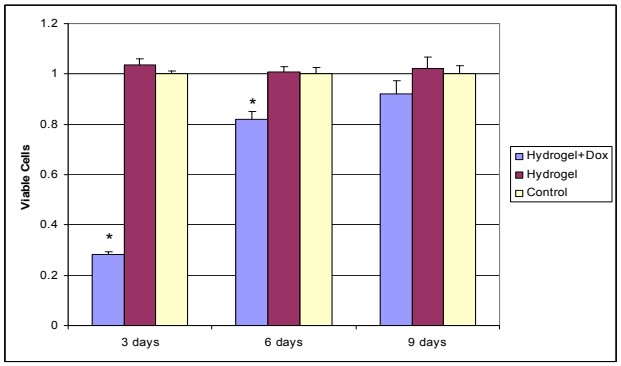

Figure 1. Cell viability after exposure to released Doxorubicin in comparison to the blank hydrogel and TCPS.

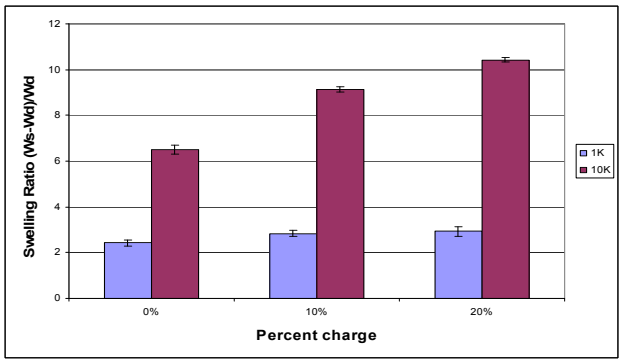

Figure 2. OPF hydrogel swelling ratio vs. hydrogel formulations.

Conclusions: Our data suggests that OPF can be used for prolonged release of anti-tumor drugs. However, the release kinetics of the drug from OPF hydrogels should be optimized for targeting bone and other cancers in vivo.

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References:

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2-Jo S. et al. Biomacromolecules 2(1):255-61 (2001).