



University
of Victoria

Graduate Studies

Notice of the Final Oral Examination
for the Degree of Master of Applied Science

of

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BSc (Islamic Azad University of Shiraz, 2015)

“Development of a Drug-Eluting 3D Bioprinted Mesh (GlioMesh) for
Treatment of Glioblastoma Multiforme”

Department of Mechanical Engineering

Thursday, April 19th, 2018

2:00 P.M.

Engineering Office Wing

Room 430

Supervisory Committee:

Dr. Mohsen Akbari, Department of Mechanical Engineering, University of Victoria (Supervisor)
Dr. Stephanie Willerth, Department of Mechanical Engineering, UVic (Member)

External Examiner:

Dr. Patrick Nahirney, Division of Medical Sciences, University of Victoria

Chair of Oral Examination:

Dr. Kim Juniper, Department of Biology, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies

Abstract

Glioblastoma multiforme (GBM) is among the most progressive and mortal cancers of the central nervous system. Maximal safe surgical resection, followed by radiotherapy accompanied with chemotherapy is the standard of care for GBM patients. Despite this intensive treatment with conventional approaches, the management of GBM remains poor. The infiltrative nature of cancer cells makes the complete tumour removal by surgery virtually impossible. In addition, the blood-brain barrier's (BBB) lack of permeability limits the number of effective chemotherapy drugs for GBM. Temozolomide (TMZ) is the most widely used chemotherapeutic agent for GBM because of its ability to pass the BBB. However, high systemic doses required to achieve brain therapeutic level, resulting in numerous side effects. The recurrence of GBM is almost inevitable due to the shortcomings of conventional methods of treatment. A great deal of effort has been focused on the development of new treatment strategies. Polymeric microspheres hold great potential to locally deliver chemotherapy drugs. However, the encapsulation of amphiphilic drug molecules such as TMZ within poly (D, L-lactide-co-glycolide) (PLGA) microspheres with conventional emulsion methods, oil-in-water (o/w), water-in-oil-in-water (w/o/w), is a major challenge. This study has focused on the development of a 3D bioprinted hydrogel-based mesh containing TMZ-loaded PLGA microspheres with high encapsulation efficiency (GlioMesh). To accomplish this, oil-in-oil (o/o) emulsion solvent evaporation technique was used to prepare PLGA microspheres loaded with TMZ. The poor solubility of TMZ in the external oil phase, liquid paraffin, resulted in obtaining encapsulation efficiencies as high as 61%. We then used the 3D bioprinting technology to embed TMZ-loaded PLGA microspheres into an alginate mesh. This provides the advantage of immobilizing the microspheres at the tumour site. Additionally, the flexibility and porosity of 3D bioprinted mesh allow for easy implantation and nutrients transportation to the brain tissue. The incorporation of polymeric microspheres within alginate fibres led to achieving an extended release of TMZ over 56 days. The functionality of GlioMesh in inducing cell cytotoxicity was evaluated by performing *in vitro* cell viability tests on U87 human glioblastoma cells. Higher cytotoxic effects were observed in the case of treatment with GlioMesh compared with the free drug due to the sustained release properties of our mesh. These data suggest that GlioMesh holds great promise to be used as an implant in the treatment of GBM.