

Biomacromolecular Granular Hydrogel Scaffolds for Wound Healing

Arian Jaberi,¹ Pejman Ghelich,³ Mohamadmahdi Samandari,³ Zaman Ataie,¹ Alireza Hassani Najafabadi,³ Ali Tamayol,^{3*} Amir Sheikhi^{1,2*}

¹ Department of Chemical Engineering, The Pennsylvania State University, University Park, PA, 16802 USA

² Department of Biomedical Engineering, The Pennsylvania State University, University Park, PA, 16802 USA

³ Department of Biomedical Engineering, University of Connecticut, Farmington, CT, 06030 USA

*Corresponding author: Ali Tamayol (atamayol@uchc.edu), Amir Sheikhi (sheikhi@psu.edu)

Wound healing rate and quality have been significantly improved with scaffold-based therapies. To further enhance these therapies, granular hydrogel scaffolds (GHS) have been developed via assembling hydrogel microparticle (HMP) building blocks that facilitate cell ingrowth and reduce inflammation. Although bulk gelatin methacryloyl (GelMA) hydrogel scaffolds have been extensively used for wound healing, the potential of GelMA GHS for this purpose remains unexplored. In this study, we fabricated GelMA HMP to form GHS and performed mechanical characterization on GHS with two different HMP sizes. The median pore equivalent diameter and compression modulus of GHS were analyzed to optimize scaffold porosity for cellular infiltration and proliferation. The effect of porosity on macrophage behavior was compared with bulk GelMA, which represents nanoporous scaffolds. The effect of porosity on wound healing was assessed *in vivo* in a murine model of full-thickness skin injury. Although the rate of wound closure was not affected by porosity, hematoxylin and eosin (H&E) staining and immunofluorescence staining 11 days post-implantation showed a thicker granulation tissue, which attested to an improved wound healing quality for GelMA GHS compared with the bulk scaffold. *In vitro* and *in vivo* results consistently show that GelMA GHS supports tissue regeneration. This study lays the foundation for engineering regenerative GelMA GHS.