Special Symposium

Biomaterials for tissue engineering applications

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Bone Angiogenesis via Bioactive Thermosensitive Injectable Hydrogels

Fatma Zehra Kocak[*1], Muhammad Yar[2], Ihtesham Ur Rehman[1]

[1]Engineering, Lancaster University, Lancaster, United Kingdom, [2]Interdisciplinary Research Centre in Biomedical Materials (IRCBM), COMSATS , University Islamabad, Lahore, Pakistan

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Introduction: Bone treatment methods comprising transplantation techniques and solid scaffold biomaterial strategies suffer from multiple invasive surgical procedures. Recently, in-situ formed injectable hydrogels have drawn attentions since they can be introduced into tissue defects via minimally invasive methods. Thermosensitive (sol-gel) hydrogels are produced as a solution, and form gel at complex tissue defects by stimuli of the natural body temperature.The lack of sufficient blood supply to tissues due to the insufficient vascularity, the ultimate bone healing in major defects remain very challenging. Therefore, there is a huge demand of development of alternative pro-angiogenic biomaterials.The main aim of this project is to develop novel chitosan based thermosensitive injectable hydrogel composites to stimulate bone angiogenesis during bone regeneration.

Experimental methods: Biodegradable chitosan (CS) matrix has been integrated with hydroxyapatite (HA) due to its inherited bioactivity. Heparin (Hep), which is a glycosaminoglycan was impregnated in CS/HA hydrogels and its angiogenesis potential investigated due to its highly anionic nature that can lead anchorage of physiologically present angiogenic growth factors.Chitosan based pH-dependent, thermoresponsive injectable solutions were produced with sol-gel technique at 4ºC by neutralizing with sodium bicarbonate ($NaHCO_3$) and hydrogels were obtained upon incubation at 37ºC. Hydrogels were evaluated for their injectability and gelation properties. In addition, rheology measurements, chemical analyses and biological analyses involving angiogenesis via Chick Chorioallantoic Membrane (CAM) assay, bioactivity studies via Simulated Body Fluid (SBF) and *in-vitro* degradation studies were also carried out.

Results and discussions: The solution injectability forces was under than the maximum manual injection force and allowing easy injection via 21 G and ticker sized needles which is suitable for orthopaedic and most dental administrations [1],[2]. Thermosetting gelation has occurred at the vicinity of body temperature and gelation was initiated from surface in 5-10 min at 37ºC. Interconnected porous hydrogels have exhibited pro-angiogenic response evaluated through CAM confirmed that the hydrogels with minimal heparin concentrations performed the best. Bioactivity studies with Simulated Body Fluid (SBF) showed needle-like carbonated apatite mineral deposition on hydrogels. In a six-weeks of *in-vitro* degradation study, hydrogels incubated in PBS and Lysozyme-PBS media had substantial weigh loss reaching up to 60 % and 70 %, respectively.

Conclusions: Bioactive and biodegradable CS/HA/Hep injectable hydrogels can find potential application to stimulate bone angiogenesis for the repair and regeneration of non-load bearing bones.

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