Statement of Purpose: Nanocomposite hydrogels have been extensively developed as functional wound dressings to promote wound healing process[1]. For antibacterial effects, silver (Ag) nanoparticles and antibiotics loaded inorganic carriers such as silica nanoparticles have been immobilized in hydrogels[2]. However, those systems can cause toxicity to cellular environment due to either high concentration of particles or fast release of drugs. In this study, calcium fluoride (CaF$_2$) nanoparticles were chosen to be along with hyaluronic acid rendering nanocomposite hydrogel system, since it can release both Ca$^{2+}$ and F$^{-}$ ions, affecting both cell proliferation and bacteria growth inhibition. In addition, the sustained release of ions from nanocomposites can be expected due to high crystallinity of CaF$_2$ and release profiles can be easily controlled by precipitation process for adjustable wound dressings.

Methods: Photocrosslinked hyaluronic acid hydrogel was immersed in CaCl$_2$ solution for overnight and subsequently dipped in NH$_4$F solution to induce CaF$_2$ precipitation within the gel. The precipitation time was controlled from 10 min to 1 hr. The surface morphology and the composition of composites was observed using FESEM and XRD, respectively, as compared with pure hydrogel. The fluoride concentrations were measured using a fluoride ion electrode. Bacteria colony test was performed using E.Coli. Cellular responses were observed by cell attachment and MTS assay using fibroblasts (L929). Wound closure was observed using incision model, treated with pure and CaF$_2$ composites.

Results: Nanoparticles were uniformly precipitated on the polymer gel, as compared with pure hydrogel. (Fig.1A). Different precipitation time affected the crystallinity and content of CaF$_2$, as depicted in Fig.1B. From fluoride ion release profiles (Fig.1C), shorter precipitation time showed faster release of fluoride, whereas 30 min and 1 hr samples performed sustained ion release. As increasing precipitation time, it showed higher effect on inhibiting bacterial growth (Fig.2A). Fibroblasts were highly stretched (Fig.2B) and proliferated on the composites, as compared with pure hydrogel. Among the composites, 10 min samples showed higher proliferation. It can be explained that large amount of calcium ions from 10 min samples have been released as well, which greatly affected cellular and bacteria proliferation. CaF$_2$ composite hydrogels showed better wound healing performance, as compared with pure hydrogel. At 6 days, CaF$_2$ samples treated wound dramatically decreased in size (Fig.3A), up to 40%, whereas pure hydrogel treated wound remained 60% (Fig.3B).

Conclusions: CaF$_2$ nanocomposite hydrogels were successfully fabricated through in-situ precipitation process. With varying the precipitation time, ion release profiles were controlled due to different crystallinity. As increasing the precipitation time, sustained release profiles were achieved, resulting positive effect on inhibiting bacteria growth and cellular responses. Therefore, CaF$_2$ composite hydrogels, as dual ion delivery systems can have great potential for highly efficient wound dressings.

Reference