



Review Article

Recent Advances In Biomaterials For Medical Applications: A Short Review of our Laboratory's Research

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Abstract

The extensive research in the biomedical area by involving tissue engineering, wound dressing and drug delivery has broadly been done by various research groups. Here, we review our laboratory's research analyses in short for giving the overview of some biomaterial-based research in medical applications, especially tissue engineering, drug delivery, and wound dressing applications.

Keywords

Biomaterials; Tissue engineering; Drug delivery

Introduction

Biomaterials for medical applications have broadly been exploited since long time and subsequently increased their utility in health-care industry that is growing rapidly due to chronic diseases, traumatic accidents, surgical reconstructions, and other health-care problems. Over the time, an extensive research has been done on biomaterials that have shown an imperative role in medical field, especially tissue engineering and drug delivery applications. In this progress, first generation of biomaterials was evolved, nearby 1960-70, with the fabrication of biomaterial devices comprising a balance between physical and mechanical properties with minimal toxicity (bio-inert) or carcinogenicity to host living tissues. Further, bio-activity and resorbable behavior were incorporated as second-generation biomaterials (e.g. use of bioactive glass and ceramics in orthopaedic and dental applications) followed by stimulating specific cell response for the living tissue regeneration as third generation of the biomaterials. Nanotechnology makes it possible to achieve improved properties of the biomaterial-based devices and drug delivery systems. Recently, architectural nanoscale features are incorporated by the researchers in developed biomaterials to mimic native extracellular matrix (ECM) to achieve proper or ideal 3D microenvironment [1-4]. However, the designing of biomaterial for complex tissue regeneration and targeted and/or controlled drug delivery is a great challenge in medical field. In cancer drug delivery, the treatment depends on the special designing of the drug molecule-carriers that may hold sufficient drug doses until the counter with specific functionalities, where drug molecules release timely and in a controlled manner [5-7].

Our laboratory developed some promising nanohybrids for some

tissue engineering applications for the improvement in physical and mechanical properties and cell-biomaterial interactions, targeted and/or stimuli-responsive behavior for cancer drug delivery, and their antibacterial behaviors for wound dressing applications. However, the selection of a suitable biomaterial is a critical and difficult choice to be used in a particular application such as tissue engineering (e.g. controlled architecture and dynamic functionality) and drug delivery (hold or encapsulate suitable amount of drugs and releasing in targeted and controlled manner). Here, we present and discuss our laboratory's research advancements for these medical applications.

Medical Applications

Tissue engineering

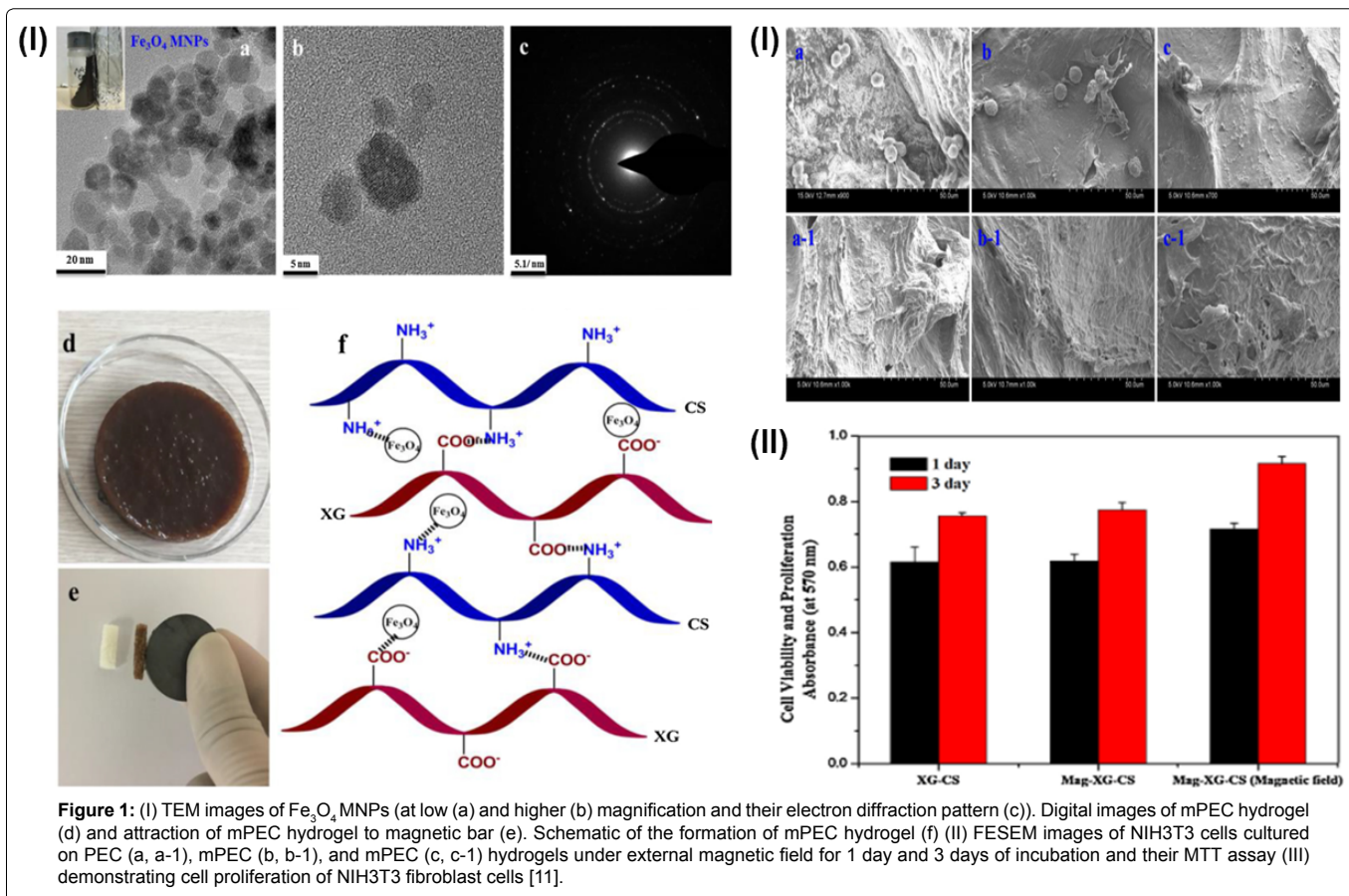
For the development of scaffolding biomaterial for tissue engineering, we investigated the effect of various crosslinking agents (calcium chloride, orthophosphoric acid, and borax) on the morphological, structural, mechanical, and cytotoxic properties of the fabricated poly (vinyl alcohol)/alginate scaffolds reinforced with cellulose nanocrystals (CNCs) that are prepared by acid-hydrolysis as described elsewhere [8]. The results showed, in case of borax, fibrous porous structure (95.2% porosity), improved mechanical stability, and good *in vitro* cell attachment and proliferation with fibroblast cells [9]. In addition, hybrid hydrogels composed of polyacrylamide (PAAm), sodium carboxymethylcellulose (CMC), graphene oxide (GO), and CNCs were prepared *via in situ* free-radical polymerization. In this study, the effect of GO (1.5 wt%) and CNCs (ranging from 2.5 to 10.0 wt%) was investigated and the obtained hybrid hydrogels showed good pseudo-plastic behavior, self-healing and shape-recovery behavior, and improved mechanical properties when reinforced with both GO and CNCs contents [10]. In another study, iron oxide magnetic nanoparticles (Fe_3O_4 MNPs) were incorporated before the self-organization of the biomaterials as xanthan gum (XG) and chitosan (CS) and prepared magnetically responsive polyelectrolyte complex (mPEC) hydrogels *via* ionic-complexation *in situ* using D-(+)-glucuronic acid L-lactone as a green acidifying agent. This incorporation of Fe_3O_4 MNPs resulted in the improvement of compressive mechanical stability, storage modulus, and good modulation and improvement in NIH3T3 fibroblast cell attachment and proliferation under an external magnetic field compared to PEC hydrogel without Fe_3O_4 MNPs (Figure 1) [11].

Further, we tried to prepare mechanically stiff and bioactive hybrid hydrogels for damaged bone tissues. In this case, CNCs and silica-based glass (SBG) were incorporated in PAAm/alginate matrix and then the effect of CNCs content (from 2.5 to 10.0 wt.%) was investigated on the properties of hybrid hydrogels. The obtained hybrid hydrogels were mechanically improved with good stiffness and showed good *in vitro* MC3T3-E1 cell attachment and proliferation without affecting their bioactivity (apatite-forming ability) in the simulated body fluid (SBF) solution (Figure 2) [12].

In other study, CNCs and SBG were incorporated in XG polymeric matrix to prepare mechanically improved hybrid scaffolds for low load-bearing bone tissues. In this case, XG provides an excellent biocompatibility and shear-thinning effect that is important for 3D microenvironment where various shear forces are applied. The

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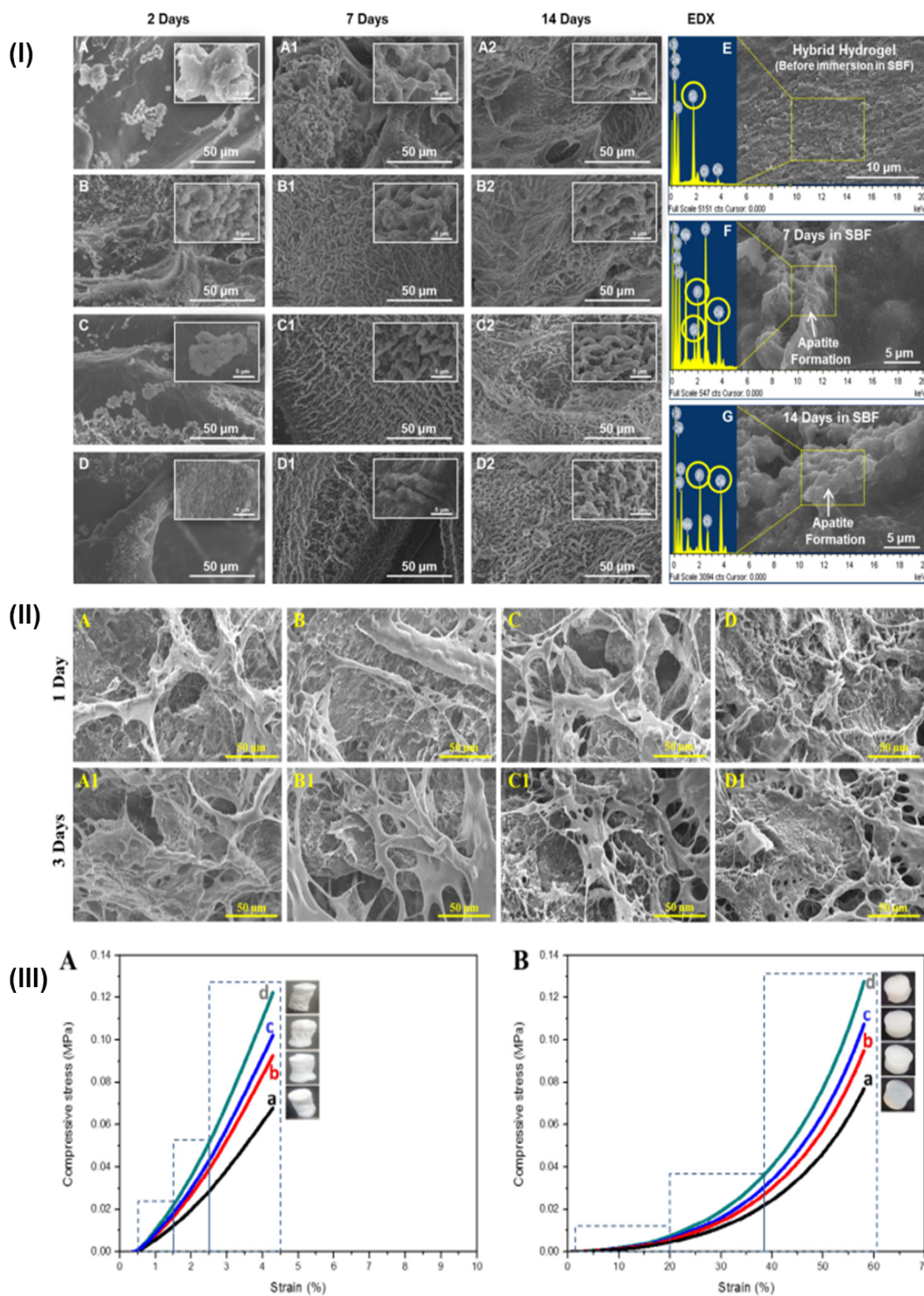


obtained hybrid scaffold showed good MC3T3-E1 cell attachment and proliferation compared to scaffold without CNCs and SBG content and this behavior was observed to improve with time and stiffness [13]. Taking this benefit of XG as biomaterial, CNCs along with halloysite nanotubes (HNTs) were incorporated in XG/alginate matrix and structure-property-performance relationship of the prepared hydrogel scaffolds was analysed. The compressive mechanical properties (in wet state) and cytocompatibility (MC3T3-E1 osteoblast cells) of the hybrid scaffolds was improved [14]. Further, by inspiring the variation charge density, low-cost, and environmentally friendly behavior of HNTs, PEC hydrogels composed of XG, CS, and HNTs using D-(+)-glucuronic acid L-lactone as a green acidifying agent were prepared and improved MC3T3-E1 cell attachment and proliferation was achieved compared to PEC hydrogels without HNTs [15].

Drug delivery

PEC hydrogels composed of XG and CS were reinforced with CNCs that improved the mechanical performance of the PEC hydrogels with increased CNCs content. In this study, 5-Fluorouracil as model chemotherapeutic drug was loaded into PEC hydrogels and showed controlled release of the model drug in CNCs reinforced PEC hydrogels compared to PEC hydrogel only. In addition, as-developed PEC hydrogels exhibited excellent cytocompatibility with NIH3T3 fibroblast cell line [16]. Further, we developed a non-cytotoxic and pH-sensitive CNCs reinforced poly (acrylamidoglycolic acid) PLGA-NC hydrogels using free-radical polymerization and further loaded with diclofenac sodium (DCF) model drug. As-developed PLGA-NC hydrogel showed significant improvement in rheological

and mechanical properties as well as good cytocompatibility with NIH3T3 fibroblast cell line. In addition, DCF-loaded PLGA-NC hydrogels exhibited much retention of the drug at pH 2 and showed maximum release in a controlled manner was observed at pH 7.4 [17]. In another study, we prepared gold nanoparticles (Au NPs, hexagonal and rod-shape structure) *in situ* in the lumen as well as the surface cage of HNTs using curcumin (CUR) as an anticancer drug and this HNTs@CUR-Au hybrid system was subsequently coated with CS as bio-adhesive polysaccharide. In this case, as-prepared Au NPs exhibited longitudinal plasmon resonance bands at around 760 and 980 nm that indicate near-infrared (NIR) responsive property of the hybrid system. The loading efficiency of CUR was estimated as 12% and released more amounts under acidic condition (pH 5.5) than basic condition (pH 7.4). As-obtained HNT@CUR-Au/CS hybrid nanoparticles showed efficient anticancer activity on MCF-7 cancer cells under intracellular cell environment (pH 5.5) than extracellular environment (pH 7.4). In addition, NIR-responsive property (Au NPs) and pH-responsive release of CUR from HNTs@CUR-Au/CS hybrid nanoparticles make it more suitable for targeted cancer drug delivery with NIR imaging [18]. We also developed a dual (pH and redox)-responsive cystamine-integrated periodic mesoporous organosilica (Cys-PMO) hybrid nanoparticles and subsequently loaded with doxorubicin (Dox) as anticancer drug for cancer drug delivery under intracellular environment. As-developed Cys-PMO hybrid nanoparticles having large surface area ($691 \text{ m}^2\text{g}^{-1}$), pore volume ($0.59 \text{ cm}^3\text{g}^{-1}$), and pore diameter (3.1 nm) exhibited mesoscopically ordered 2D hexagonal (P6 mm) symmetry with cylindrical shape. These Cys-PMO hybrid nanoparticles were capable



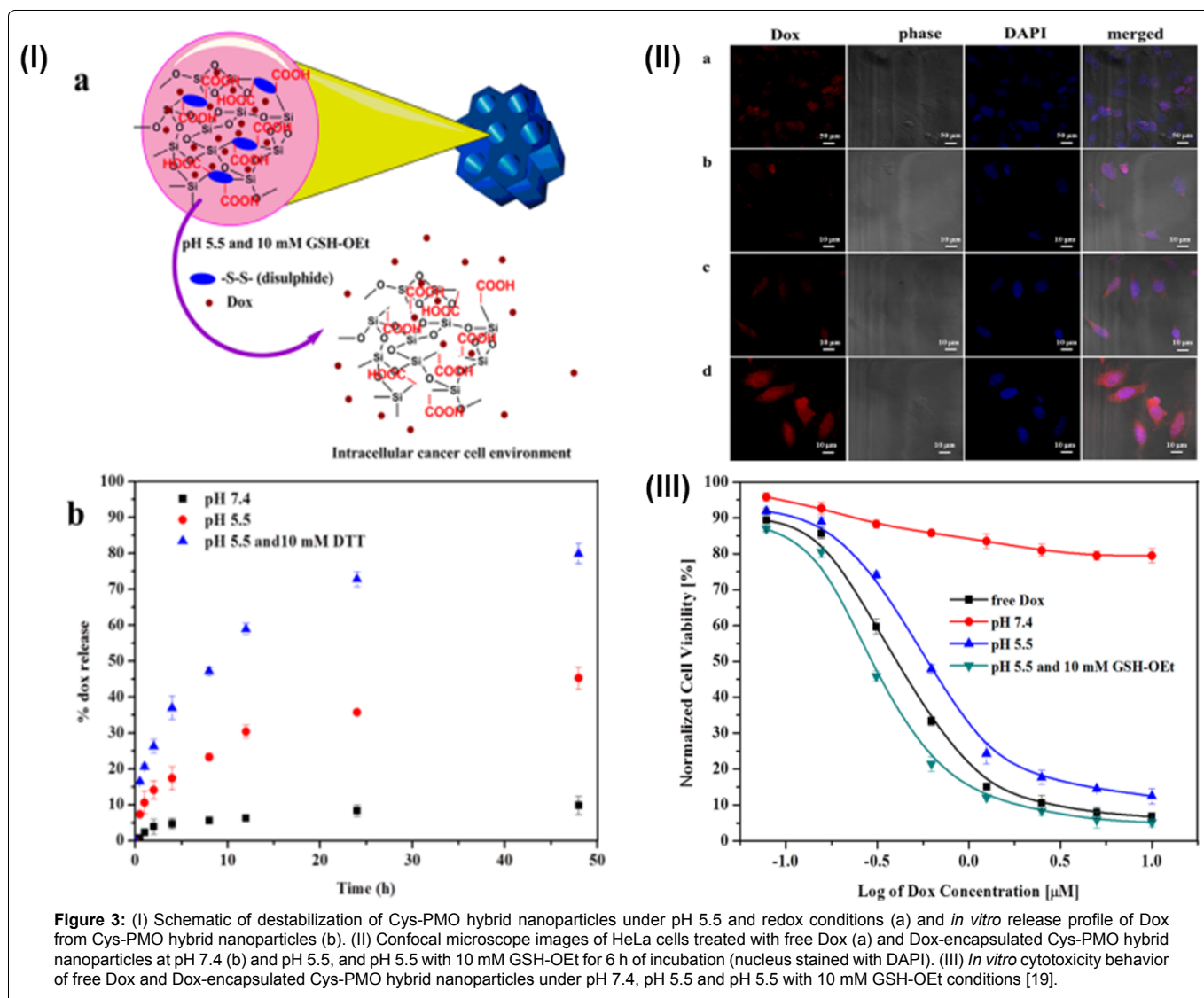
of holding a high Dox content (50.6% of Cys-PMO content) at an optimized amount of Dox (20 mg) and avoided premature release of drug under extracellular environment. Dox-encapsulated Cys-PMO hybrid nanoparticles showed significantly higher cytotoxicity with HeLa cells under intracellular acidic pH and redox-environment. Further, this behavior can be supported by confocal microscope images that exhibit the colocalization of Dox-encapsulated Cys-PMO hybrid nanoparticles inside HeLa cells and release Dox directly to the nucleus of HeLa cells under intracellular pH and redox conditions (Figure 3) [19].

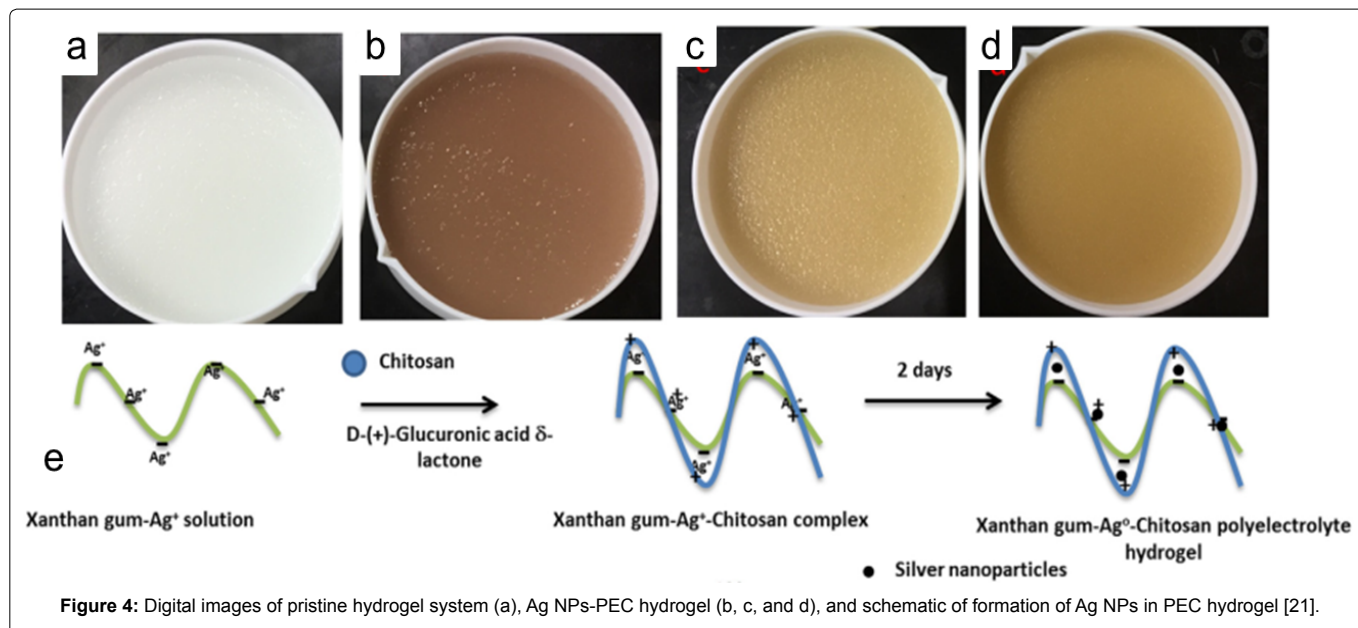
Wound dressing

Silver nanoparticles (Ag NPs) have shown a great potential in wound dressing applications and extensively used for antibacterial properties. For wound dressing applications, we have developed silver nanoparticles (Ag NPs) impregnated tragacanth gum (TG)-based hydrogel system using acrylamide as monomer using free-radical polymerization. In this case, a uniform distribution of Ag NPs in TG hydrogel network was impregnated through *in situ* reduction of Ag ions using Terminalia chebula (TC) leaf extract, where TG

acted as efficient stabilizer or capping agent to prepare uniform distribution of spherical Ag NPs (average size of around 5 nm) within the hydrogel network. These as-prepared Ag NPs nanocomposite hydrogel systems (TG0, TG1, TG2, and TG3 for 3, 4, 6.4, and 8.1 wt% of Ag NPs) exhibited excellent antibacterial behavior towards *E. coli* and *B. subtilis* bacteria and can potentially be used as wound dressing biomaterial [20]. In another study, we prepared these size controlled Ag NPs (spherical shape and diameters around 5-20 nm) in PEC hydrogels composed of XG and CS using green method without the use of any organic solvent or reagent (Figure 4). Ag NPs incorporated PEC hydrogels showed a strong antibacterial behavior towards *E. coli* and *S. aureus* without affecting cell attachment and proliferation of NIH3T3 fibroblast cells significantly. These Ag NPs-PEC hydrogels exhibited a great potential in wound dressing as well as tissue engineering applications [21].

Further, we prepared sodium hyaluronate stabilized CUR-Ag hybrid nanoparticles with spherical shape and 5-12 nm size range in the water-ethanol mixture and then, a fibrous filter paper was uniformly impregnated with these CUR-Ag hybrid nanoparticles and coated with CS *via* polyelectrolyte complexation. This CUR-Ag





impregnated CS coated filter paper showed excellent antibacterial behavior towards *E. coli* bacteria compared to HA stabilized CUR only and can potentially be used in medical applications such as wound dressing applications [22].

Challenges and Future Perspectives

Although various biomaterials-based devices have been developed by considering different and specific parameters for successful tissue regeneration, but not succeeded to achieve suitable and dynamic composition of native 3D microenvironment of tissues. Actually, most of the tissue regeneration studies are limited to the periphery of the developed scaffolding biomaterials upon implantation due to the lack of sufficient and timely vascularization of the biomaterial for the optimal formation and integration of the tissue. This is due to mismatch of the characteristics of the scaffolding biomaterials and the formation of new tissues. In the last two decades, tissue engineering/regenerative medicine and drug delivery field has progressed tremendously for possibly successful clinical translational of biomaterial-based devices or drug delivery systems for societal needs. Nevertheless, various key challenges remain to be overcome to achieve this clinical translational [23-25]. In tissue engineering, the main challenge is to provide the proper gradual transform (time-dependent) and maturation of the cell-engineered implant during *in vivo* through cellular interaction, self-organization of the cells, and/or gradual deposition of the matrix and following to the formation of new functional tissue within a particular time span [26-28]. In addition, drug delivery, especially cancer drug delivery, needs a special design of the drug-carriers that hold sufficient amounts of drugs until the interaction with specific entities or functionalities and release drug molecules timely and in a controlled manner. In the last decade, three-dimensional (3D) printing technology has been evolved and highly beneficial in these areas to overcome these drawbacks [26-29]. Also, various biomaterials/nanomaterial types have already been explored for wound healing, but it is far from common clinical practice and commercialization and needs for experimental and preclinical studies for wound care (especially chronic wound healing) [30].

References

- Bhat S, Kumar A (2013) Biomaterials and bioengineering tomorrow's healthcare. *Biomater* 3: e24717.
- Kumar A, Han SS (2017) PVA-based hydrogels for tissue engineering: A Review. *Int J Polym Mater Polym Biomater* 66: 159-182.
- Kumar A, Negi YS, Choudhary V, Bhardwaj NK (2014) Microstructural and mechanical properties of porous biocomposite scaffolds based on poly (vinyl alcohol), nano-hydroxyapatite and cellulose nanocrystals. *Cellulose* 21: 3409-3426.
- Kumar A, Negi YS, Choudhary V, Bhardwaj NK, Han SS (2017) Morphological, mechanical, and *in vitro* cytocompatibility analysis of poly (vinyl alcohol)-silica glass hybrid scaffolds reinforced with cellulose nanocrystals. *Int J Polym Anal Charact* 22: 139-151.
- Zhang Y, Sun T, Jiang C (2017) Biomacromolecules as carriers in drug delivery and tissue engineering. *Acta Pharm Sin B* 8: 34-50.
- Saghazadeh S, Rinoldi C, Schot M, Kashaf SS, Sharifi F, et al. (2018) Drug delivery systems and materials for wound healing applications. *Adv Drug Deliv Rev*.
- Sheikhpour M, Barani L, Kasaeian A (2017) Biomimetics in drug delivery systems: A critical review. *J Control Release* 253: 97-109.
- Kumar A, Negi YS, Choudhary V, Bhardwaj NK (2014) Characterization of Cellulose Nanocrystals Produced by Acid-Hydrolysis from Sugarcane Bagasse as Agro-Waste. *J Mater Phys Chem* 2: 1-8.
- Kumar A, Lee Y, Kim D, Rao KM, Kim J, et al. (2017) Effect of crosslinking functionality on microstructure, mechanical properties, and *in vitro* cytocompatibility of cellulose nanocrystals reinforced poly (vinyl alcohol)/ sodium alginate hybrid scaffolds. *Int J Biol Macromol* 95: 962-973.
- Kumar A, Rao KM, Han SS (2018) Mechanically viscoelastic nanoreinforced hybrid hydrogels composed of polyacrylamide, sodium carboxymethylcellulose, graphene oxide, and cellulose nanocrystals. *Carbohydr Polym* 193: 228-238.
- Rao KM, Kumar A, Han SS (2017) Polysaccharide-based magnetically responsive polyelectrolyte hydrogels for tissue engineering applications. *J Mater Sci Technol*.
- Kumar A, Rao KM, Han SS (2017) Synthesis of mechanically stiff and bioactive hybrid hydrogels for bone tissue engineering applications. *Chem Eng J* 317: 119-131.
- Kumar A, Rao KM, Kwon SE, Lee YN, Han SS (2017) Xanthan gum/bioactive silica glass hybrid scaffolds reinforced with cellulose nanocrystals: Morphological, mechanical, and *in vitro* cytocompatibility study. *Mater Lett* 193: 274-278.

14. Kumar A, Rao KM, Han SS (2017) Development of sodium alginate-xanthan gum based nanocomposite scaffolds reinforced with cellulose nanocrystals and halloysite nanotubes. *Polym Test* 63: 214-225.
15. Rao KM, Kumar A, Han SS (2018) Polysaccharide based hydrogels reinforced with halloysite nanotubes via polyelectrolyte complexation. *Mater Lett* 213: 231-235.
16. Rao KM, Kumar A, Han SS (2017) Polysaccharide based bionanocomposite hydrogels reinforced with cellulose nanocrystals: Drug release and biocompatibility analyses. *Int J Biol Macromol* 101: 165-171.
17. Rao KM, Kumar A, Han SS (2017) Poly (acrylamidoglycolic acid) nanocomposite hydrogels reinforced with cellulose nanocrystals for pH-sensitive controlled release of diclofenac sodium. *Polym Test* 64: 175-182.
18. Rao KM, Kumar A, Suneetha M, Han SS (2018) pH and near-infrared active; chitosan-coated halloysite nanotubes loaded with curcumin-Au hybrid nanoparticles for cancer drug delivery. *Int J Biol Macromol* 112: 119-125.
19. Rao KM, Parambadath S, Kumar A, Ha CS, Han SS (2017) Tunable Intracellular Degradable Periodic Mesoporous Organosilica Hybrid Nanoparticles for Doxorubicin Drug Delivery in Cancer Cells. *ACS Biomater Sci Eng* 4: 175-183.
20. Rao KM, Kumar A, Rao KSVK, Haider A, Han SS (2018) Biodegradable Tragacanth Gum Based Silver Nanocomposite Hydrogels and Their Antibacterial Evaluation. *J Polym Environ* 26: 778-788.
21. Rao KM, Kumar A, Haider A, Han SS (2016) Polysaccharides based antibacterial polyelectrolyte hydrogels with silver nanoparticles. *Mater Lett* 184: 189-192.
22. Kummara MR, Kumar A, Soo HS (2017) Development of antibacterial paper coated with sodium hyaluronate stabilized curcumin-Ag nanohybrid and chitosan via polyelectrolyte complexation for medical applications. *Mater Res Express* 4: 115401.
23. Amini AR, Laurencin CT, Nukavarapu SP (2012) Bone tissue engineering: recent advances and challenges. *Crit Rev Biomed Eng* 40: 363-408.
24. Liu Y, Lim J, Teoh SH (2013) Review: development of clinically relevant scaffolds for vascularised bone tissue engineering. *Biotechnol Adv* 31: 688-705
25. Saravanan S, Leena RS, Selvamurugan N (2016) Chitosan based biocomposite scaffolds for bone tissue engineering. *Int J Biol Macromol* 93: 1354-1365.
26. An J, Teoh JEM, Suntornnond R, Chua CK (2015) Design and 3D printing of scaffolds and tissues. *Engineering* 1: 261-268.
27. Stanton MM, Samitier J, Sánchez S (2015) Bioprinting of 3D hydrogels. *Lab Chip* 15: 3111-3115.
28. Khoo ZX, Teoh JEM, Liu Y, Chua CK, Yang S, et al. (2015) 3D printing of smart materials: a review on recent progresses in 4D printing. *Virtual Phys Prototyp* 10: 103-122.
29. Kumar A, Han SS (2016) Emergence of bioprinting in tissue engineering: A mini review. *Adv Tissue Eng Regen Med* 1: 00013.
30. Rajendran NK, Kumar SSD, Houreld NN, Abrahamse H (2018) A review on nanoparticle based treatment for wound healing. *J Drug Deliv Sci Technol* 44: 421-430.

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