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Editorial
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Polymeric Hydrogels for Therapeutic Delivery

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Editorial

The primary goal in developing therapeutic delivery systems is to improve the stability of therapeutic agents against chemical/enzymatic degradation, while prolong, localize, enhance drug efficacy and minimize side effects [1]. For these purposes, a variety of polymeric based drug delivery systems including nanoparticles [2], micelles [3], conjugates [4], nanofibers [5], microneedles [6], nanogels [7] and hydrogels [8], have been developed with different focuses. For example, nanoparticles were used as drug carriers to alter the biodistribution of chemotherapeutics [9], conjugation of poly(ethylene glycol) were used to improve drug pharmacokinetics [10], and microneedles were used to enhance transdermal drug delivery for improved patient compliance, sustained release and avoidance of gastric irritation [11]. In recent years, significant efforts have been devoted to develop polymeric hydrogel delivery systems because of their potential over alternatives including versatility in design [12,13], tunability for various drug release profiles [14,15], high permeability and biocompatibility [16,17].

Hydrogels by definition are three-dimensional hydrophilic polymer networks that are capable of containing large amounts of water or biological fluids while maintaining their semisolid porous morphology [18]. The first hydrogels formulated specifically for the use in healthcare, poly(2-hydroxyethyl methacrylate) (PHEMA), was developed by Wichterle and Lim in 1960 [19]. The hydrogel technologies since then are commonly used for a wide range of biomedical applications and clinical practice, including tissue engineering [20], regenerative medicine [21], controlled drug delivery [22], and smart diagnostics [23]. In the drug delivery applications, the benefits of hydrogel delivery systems are mainly pharmacokinetic [24]. By adjusting the mesh size of hydrogel networks, the diffusion coefficient of drug payload can be changed. The loaded drug can either be slowly eluted, maintaining a high local concentration in the surrounding tissues over an extended period to exert their actions, or it can be fast released to achieve a short-term high local concentration. Hydrogels are also soft and pliable in nature,which minimizes mechanical irritation and damage to the surrounding tissue after implantation, making them promising candidates for *in vivo* biomedical application [25].

Hydrogels can be classified as natural, synthetic or semisynthetic, according to the nature of their composite polymers. Synthetic polymers, such as poly(ethylene glycol)(PEG), poly(vinyl alcohol) (PVA), poly(2-hydroxyethyl methacrylate) (PHEMA), poly(acrylic acid) (PAA), poly(methyl acrylate) (PMA), polyacrylamide (PAM) and poly(N-isopropyl acrylamide) (NIPAM) have been used to form hydrogels with variable drug release properties and mechanical strengths [26]. However, most synthetic polymer hydrogels are limited in the use of medical applications because they are non-degradable *in vivo*. Natural polymers, especially extracellular matrices (ECM) fibrous proteins, such as elastin and collagen, exhibit many advantageous characteristics for tissue regeneration, controlled release of biomolecules or regenerative medicine. Compared to synthetic polymers, the ECM fibrous proteins are generally biocompatible and fully degradable *in vivo*, which is critical for many biomedical needs [16,17]. The incorporation of therapeutics into protein hydrogels are also relatively easier through diverse amino acid chemistries, or via the formation of well-defined supramolecular structures, such as β-sheets, α-helices and β-turns. Moreover, protein hydrogels can be designed genetically to contain functional domains for cell adhesion, growth factor binding and degradation through genetic protein engineering approaches without further chemical modification. These unique properties of protein-based hydrogels have made them valuable biomaterials in the development of controlled delivery system.

Recent trend in hydrogel design have revolutionized from static to stimuli-responsive system to address needs for controlled release systems [27]. These stimuli-responsive 'smart' hydrogels are capable of responding to environmental stimuli such as temperature, pH and certain biological signals with spatiotemporal precision. For example, genetic engineered silk-elastin-like proteins were developed to form stimuli-responsive hydrogels via enzymatic crosslinking to form elastin

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networks [28]. The resulting SELP hydrogels exhibited significant swelling ratios as well as significant reversible changes in optical transparency, mechanical properties and hydrogel pore size upon exposure to thermal triggers, showing great potential for swelling-controlled release of drugs in various conditions. The development of dynamic protein hydrogel systems will open up new possibilities for the use of hydrogels as therapeutic vehicles for target delivery.

Despite many advantageous properties, hydrogel therapeutics delivery systems also have several limitations. One set of major challenges relates to expanding the types of kinetic release profiles for long-term release applications. Other challenges include improvement in the delivery of hydrophobic molecules and more sensitive molecules such as proteins, antibodies, or nucleic acids which can be deactivated or unfolded by interactions with the hydrogel delivery vehicle. Progress on any or all of above challenges will greatly expand the potential of hydrogel therapeutics delivery systems to deliver designed drugs at a desired release rate and location *in vivo*.

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