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Injectable polymeric hydrogels for the delivery of therapeutic agents: A review

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ABSTRACT

Since drug delivery systems have become one of the most promising areas of human health related research, the applications of biomaterials such as hydrogels have been widely investigated. Possessing unique hydrophilic, biocompatible network structures and the ability to form solid-like gel states once administered, injectable hydrogels facilitate the encapsulation and release of therapeutic agents, including drugs, proteins, genes and cells, in a controllable manner. A wide and diverse range of techniques have been used to generate hydrogels, from chemical cross-linking, such as photo-polymerization, click chemistry, enzyme-catalyzed reactions, Schiff's base reactions, and thiol-based Michael reactions, to physical cross-linking induced by temperature, pH, ionic interaction, guest–host inclusion, stereo-complexation or complementary binding. This review covers the utilization of various injectable hydrogel systems for the delivery of therapeutic agents from the viewpoint of cross-linking methods.

1. Introduction

As scientific research has grown, an enormous number of studies about biomaterials related to human health have been carried out. On the 50th anniversary of the European Polymer Journal, we are honored to give a brief review of hydrogels, one of the major subjects of biomaterials research. Since the first report of hydrogels by Wichterle and Lim as water-swollen three-dimensional networks, these materials have attracted remarkable interest from the scientific research community [1]. A hydrogel is a three dimensional structure that can absorb and contain a high amount of water or biological fluid [2]. Its polymer network structure can be formed by chemical cross-linking, physical cross-linking or both simultaneously. The chemical nature, network morphology and equilibrium swollen state of hydrogels are responsible for several important properties such as mechanical strength and internal and external transport [3]. Moreover, the large volume of water that they can absorb and their soft consistency are some of the main reasons for some of the advantageous properties of hydrogels, such as biocompatibility and an ability to mimic the extracellular matrix environment. Thanks to these favorable characteristic, hydrogels have become potential candidates for many biomedical and pharmaceutical applications [4–9]. Typical applications of hydrogels include tissue engineering [10–12], soft contact lenses [13], wound-healing [14], sensors [15], mucoadhesives [16] and bioactive factor delivery systems [17,18]. From their very early and relatively simple application as contact lenses, hydrogels have been widely developed and significantly used for more complicated applications, particularly in tissue engineering and the controlled delivery of therapeutic agents. Proteins or drugs can benefit greatly from hydrogel-based controlled release systems. Possessing a

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water-swollen porous structure, which can be controlled by the density of cross-links, hydrogels provide a well-designed and friendly environment for encapsulated bioactive factors. Hopefully, after loading into a gel matrix, proteins or drugs will be released with a concentration in the plasma that falls within the therapeutic range. Various delivery strategies were detailed in a recent review paper by Alsberg et al. [18].

Hydrogels can be classified in a number of ways, such as according to their original source (natural and synthetic polymer), structure (inter-penetrating network, copolymer network, homopolymer network, and double network), cross-linking method (chemically and physically), charge (anionic, cationic, amphoteric, and non-ionic) and biodegradability (non-degradable and degradable). Previously, hydrogel research mainly focused on chemically cross-linked networks that formed a permanent gel before administration [5]. In those implantable permanently cross-linked systems, the use of toxic catalysts and cross-linker monomers could damage and denature fragile molecules such as proteins, drugs or cells. Moreover, there was a demand for homogeneous encapsulation with biological molecules and a minimally invasive operation. Hence, to overcome these drawbacks, recent hydrogel developments have concentrated on *in situ*-forming hydrogels that can gelate spontaneously in physiological conditions after injection. As well as *in situ*-forming systems, a subcategory of preformed gels which is identified as shear-thinning hydrogel can also be employed by injection method, which is preferable for use in therapeutic agent delivery. Although this review focuses mostly on the applications of injectable *in situ*-forming systems, the utilizations of shear-thinning hydrogels are still addressed. *In situ*-forming hydrogels can be prepared by applying UV radiation, adding non-reversible covalent bonds or using self-assembling polymers. Among these, the most interesting are self-assembling hydrogels, which can be fabricated by various cross-linking methods, including physical gelling, chemical cross-linking and a dual mechanism. The cross-linking process significantly changes the properties of polymers, such as the molecular mass, mechanical strength, and resistance to heat and solvents [19]. Either physical or chemical cross-linking creates the three-dimensional structure of a hydrogel, which allows the encapsulation and release of drugs and biomolecules. Hydrogels from the viewpoint of cross-linking methods have been reviewed elsewhere [20]. Physically cross-linked hydrogels usually have poor mechanical properties that may not satisfy the requirements of complicated applications in which toughness and strength are demanded. In contrast, a drawback of *in situ*-forming chemical hydrogels is the possible dissolution of the hydrogel immediately after injection due to a slow gelation kinetic. To combine the mechanical strength of a chemical gel and the fast gel formability of a physical gel, synergistic dual gelling hydrogels have recently been developed. In this review, we present the recent progress in this state-of-the-art research field, with a particular focus on injectable chemical, physical and dual gelling hydrogels for therapeutic agent delivery. Moreover, our recent works on the development of pH/temperature-sensitive hydrogels are also described in this review.

2. Chemically cross-linked hydrogels

Chemically cross-linked hydrogels represent a hydrogel class that can change from a liquid state to a gel state by forming new covalent bonds in a polymer network through chemical reactions. These types of hydrogels have typically been used for implantable applications. Because injectable devices thereafter received considerable attention, chemical cross-linking techniques have also been applied in such systems, particularly, *in situ*-forming hydrogels. Reactions can take place by various mechanisms, such as redox reactions, photo-polymerization, click chemistry, Michael reactions, Schiff's base reactions, enzymatic reactions, or disulfide-forming reactions. New covalent bonds formed from the reaction construct a polymeric three-dimensional network structure in which water can be entrapped, and therapeutic agents or living cells can be encapsulated. Each type of reaction involves a preparation process, mechanical strength, a catalyst, hydrolytic stability and other specific properties of hydrogels. In this section, some of the main strategies for fabricating injectable chemically cross-linked hydrogels will be addressed.

2.1. Photocrosslinked hydrogels

Photopolymerization has been a cross-linking technique with several advantages, including low energy and free solvent requirements, a rapid reaction with mild conditions. Additionally, thanks to spatio-temporal control ability, photo-polymerizable hydrogels have been exploited for a decade in biomedical and pharmaceutical applications, mostly in tissue engineering [21,22]. Photo-crosslinked systems can be formulated from aqueous solutions of polymers containing photo-sensitive molecules and a catalyst for polymerization. Upon exposure to an external irradiation source such as UV or visible light, the photo-initiator can be decomposed, thus forming free radicals and catalyzing the polymerization. Polymers used for photocrosslinking reactions usually have methacrylate or acrylate groups, which undergo rapid polymerization in the presence of light irradiation (Fig. 1). This approach allows for the spatial control of the cross-linked network. Moreover, the gelation rate can also be controlled timely, resulting in the formation of patterned structured hydrogels for designed release profiles. Some studies on the controlled delivery of proteins, genes and drugs are reported in this section.

An early example of an injectable photocrosslinked hydrogel for bioactive agent delivery was introduced by Hubbell et al. in 1993 [23]. Polyethylene glycol was copolymerized with α-hydroxy acids such as polylactic acid (PLA) or polyglycolic acid (PGA) and modified with an acrylate group to yield a water-soluble copolymer that could be photocrosslinked under visible light in the presence of an initiator. Gelation occurred rapidly under mild conditions without any excess heating or local toxicity. The potential for protein delivery was studied using an albumin protein model and resulted in a continuous release of up to