Journal of Controlled Release 267 (2017) 57–66

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

# Injectable hydrogels for sustained release of therapeutic agents☆

Thavasyappan Thambi, Yi Li, Doo Sung Lee*

*School of Chemical Engineering, Theranostic Macromolecules Research Center, Sungkyunkwan University, Suwon 440-746, Republic of Korea*

ARTICLE INFO

*Keywords:*
Biodegradable copolymers
pH- and temperature-responsive copolymers
Therapeutic agents
Controlled release
Hydrogels

ABSTRACT

Hydrogels are natural or synthetic polymer networks that exhibit high water absorbent capacities and have been used as scaffolds for tissue engineering or as delivery carriers for therapeutic agents and cells. Owing to their tunable physicochemical properties, hydrogels can provide spatial and temporal control over the release of loaded therapeutic agents, including chemotherapeutic drugs, proteins or cells. In particular, *in situ*-forming injectable hydrogels, the state-of-the-art clear free flowing polymer solutions that transform to viscoelastic gels upon exposure to stimuli including pH, temperature, light, enzymes and magnetic field, have been widely studied as delivery carriers for therapeutic agents. Therapeutic agents can be easily mixed with the free flowing polymer solutions and injected into the subcutaneous tissue or target site that could form a viscoelastic gel and act as therapeutic agents release depot. Hence, injectable hydrogels paid attention as sustained delivery vehicles. In this review, we systematically summarize the development of biocompatible, biodegradable, and pH- and temperature-responsive injectable hydrogels for sustained release of therapeutic agents. The key factors responsible for *in situ* gelation, interaction between polymers and therapeutic agents, and controlling the degradation of hydrogel matrix, are discussed. Advantages and perspectives of pH- and temperature-responsive injectable hydrogels in sustained therapeutic agents release are highlighted.

## 1. Introduction

Hydrogels are three-dimensional polymeric networks that are frequently used as scaffolds for tissue regeneration or as delivery vehicles for therapeutic agents and cells [1–3]. Given their unique structure, hydrogels could absorb a large volume of water or biological fluids. The presence of high water content in the hydrogels can provide excellent biocompatibility, capability to encapsulate hydrophilic drugs, and structural similarity to native extracellular matrix (ECM) or tissues [4,5]. However, subcutaneous implantation of traditional preformed hydrogel is rather costly and requires costly surgical intervention with poor patient compliance. Thus, attention has been paid to the smart hydrogels in which therapeutic agents containing polymer precursors are administered into the body using a syringe in a minimal invasive manner, triggering gelation inside the body in response to the environmental changes [6]. In particular, *in situ*-forming injectable hydrogels, the state-of-the-art clear free-flowing polymer sols that can transform into a non-flowing viscoelastic gel when exposed to physical or chemical stimuli, possess enormous potential in medicine [7–9]. The sol-to-gel phase transition properties of injectable hydrogels allow easy implantation of polymeric materials into the body in a minimally invasive manner using a syringe or catheter [10,11]. Such injectable hydrogels assembled *via* chemical and physical means are prepared using various synthetic polymers and the chemical structure of the injectable hydrogels is modular [8]. Their degradation rate, product and time can be controlled by means of the hydrophilic and hydrophobic balance or cross-linking density in the copolymers [9,12–14].

*In situ*-forming injectable hydrogels are prepared by physical or chemical cross-linking in response to various stimuli [15]. In comparison with chemically cross-linked permanent hydrogel networks, prepared using Michael addition, Schiff base, photo-polymerization reactions, injectable hydrogels prepared using physical cross-linking method are reversible [16–18]. Inter and intramolecular hydrophobic interactions induced by the physical stimuli are involved in physical cross-linked hydrogels [10,19,20]. In addition, ionic interaction, hydrogen bonding, host-guest interaction and stereo complexation are also employed to develop physically cross-linked hydrogels [21–23]. Various features of hydrogels including size, shape, architecture, and chemical/physical function can control the release of therapeutics. The solid-like hydrogel networks composed of hydrophilic or amphiphilic polymers can possess tunable rheological properties ranging from 0.5 kPa to 5 MPa [24]. The high stiffness in the hydrogel networks impede the penetration and premature release of loaded therapeutics agents. These properties are critical for certain macromolecular

☆ This manuscript is submitted for the special issue on Korean Academy of Science and Technology Symposium for Young Scientists in Drug Delivery.

* Corresponding author.
*E-mail address:* dslee@skku.edu (D.S. Lee).

http://dx.doi.org/10.1016/j.jconrel.2017.08.006
Received 11 May 2017; Received in revised form 31 July 2017; Accepted 3 August 2017
Available online 04 August 2017
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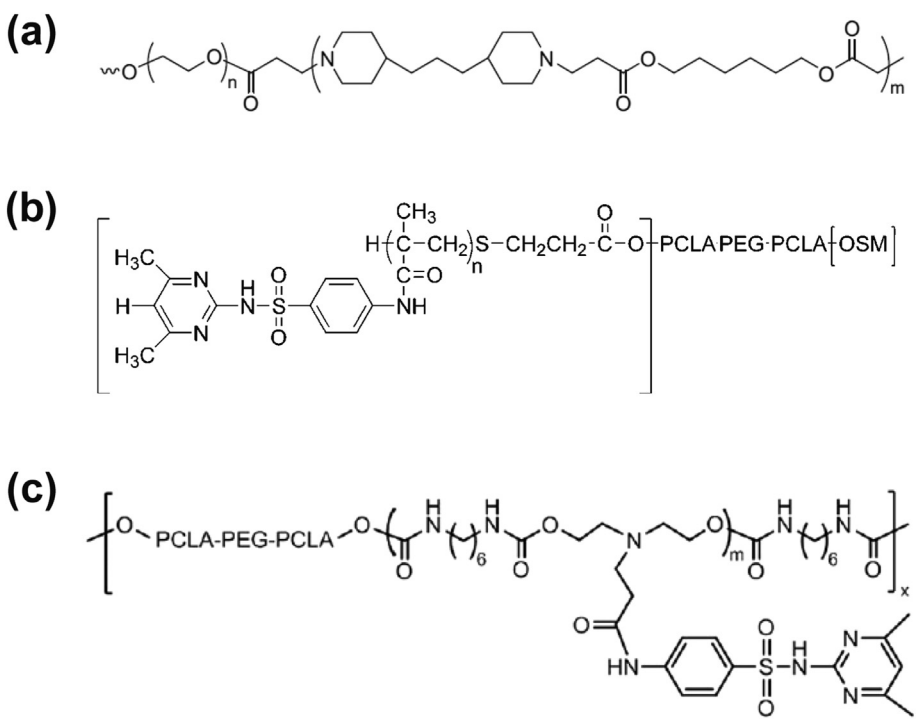


**Fig. 1.** Chemical structure of (a) PAE-PEG-PAE, (b) OSM-PCLA-PEG-PCLA-OSM, and (c) PUASM copolymers.

proteins such as human growth hormone (hGH) and insulin and makes injectable hydrogels as suitable delivery vehicles for the delivery of macromolecules. The hydrogel networks contain porous structures, the size of which is referred to as the mesh size. Controlling the mesh size in the hydrogel network is essential for sustained therapeutics delivery [24]. In addition to the mesh size, chemical and physical interactions occurs between therapeutic agents and polymer chains, and also the binding interaction between therapeutic agents and polymer chains play a crucial role in controlled drug delivery.

In this review, we summarize the development of biocompatible and biodegradable and *in situ*-forming injectable hydrogels for sustained release of therapeutic agents. We mainly focus on pH- and temperature-sensitive *in situ*-forming injectable hydrogels, giving special attention to the novel pH- and temperature-sensitive polymers developed in our laboratory based on poly(amino urethane), poly(amino ester urethane), poly(amino urea urethane), poly(amino carbonate urethane), and poly (carbonate sulfamethazine) copolymers. Unlike temperature-responsive copolymers, which exhibit needle clogging issue, pH- and temperature-sensitive copolymers elegantly injected into the deep tissues without needle clogging. The key factors responsible for gelation, interaction between polymers and therapeutic agents, and controlling the degradation of hydrogel matrix are discussed. Advantages and perspectives of pH- and temperature-responsive injectable hydrogels in sustained therapeutic agents release are highlighted.

## 2. pH- and temperature-responsive copolymers

In general, the pH- and temperature-responsive polymers consist of pH-responsive ionizable functional groups that either accept or release protons, and temperature-responsive swelling and de-swelling hydrophobic functional groups [25–29]. At high temperature, the hydrophobic group interact each other and the water exposed in the polymer chains are collapsed. At the above and below predetermined pH, the structural properties of the pH-responsive copolymers are dramatically altered, resulting in change of hydrodynamic diameter and surface charge of the polymeric chains. The rapid change in the net charge of polymer chains in response to the pH causes an alteration of the hydrodynamic volume or confirmation of the polymer chains. There are three distinct classes of pH- and temperature-responsive copolymers, including cationic, anionic and amphoteric copolymers. They are useful for the design of physiological stimuli-responsive injectable hydrogels. The structural characteristics of the copolymers are discussed below.

### 2.1. pH- and temperature-responsive cationic copolymers

The pH- and temperature-responsive biocompatible and biodegradable poly(*β*-amino ester)s (PAE) consist of tertiary amine groups have been widely used in injectable hydrogel system because of their ability to form hydrogen bonding and ionic interactions with negatively charged therapeutic agents including DNA and hGH (Fig. 1a) [30–32]. The PAE was synthesized by Micahel addition polymerization reaction using bis(secondary amines) or primary amines and bis(acrylate ester). The PAE polymer undergoes sol-to-gel phase transition by increasing the pH from acidic to basic. At low pH, the PAE polymer was soluble owing to the ionization of tertiary amine groups and exhibited a sol state, upon increasing the pH deionization of tertiary amines led to the increase in hydrophobicity and transformed to a gel. The PAE polymers are biocompatible and degrade into non-toxic small molecule by-products.

### 2.2. pH- and temperature-responsive anionic copolymers

Sulfonamide derivatives containing copolymers are the most commonly used pH- and temperature-responsive copolymers for biomedical applications (Fig. 1b) [33,34]. Based on the pendent substituents in the poly(sulfonamide) copolymers, the pKa can vary from 3 to 11. At high pH, the acidic hydrogen atom of -$SO_2$-NH- accepts an electron, and the sulfonamide groups are ionized. As a result, poly(sulfonamide) based copolymers become hydrophilic and the presence of electrostatic repulsion between the sulfonamide groups allow the easy flow of copolymers in aqueous solutions. On the other hand, the sulfonamide groups are de-ionized at low pH and the poly(sulfonamide) copolymers became hydrophobic. These anionic copolymers allow the easy complexation of cationic proteins and the hydrogel prepared using these polymers allow the sustained release of cationic proteins.

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