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Recent progress of in situ formed gels for biomedical applications

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ABSTRACT

With the rapid progress of biomedical technology, hydrogels that can be prepared under bio-friendly conditions are urgently needed. In situ gelling systems have been extensively investigated with the aim of being applied for minimally invasive drug delivery or injectable tissue engineering. In a premixed state of an aqueous solution, the system contains drugs or cells and other excipients. Chemical or physical triggering processes produce a hydrogel in situ. During the solution-to-gel transition process, all of the ingredients in the system form a matrix, where the drugs can be slowly released or within which cells/stem cells can grow in a specifically controlled manner. Basically, the triggering process and transition should not damage the incorporated elements, including pharmaceuticals, and cells, including stem cells. In addition, once it is formed, a hydrogel should provide a compatible microenvironment for the drugs and cells. Finally the hydrogel should be eliminated from the site after its role as a scaffold or depot is complete. In this review, in situ gelling systems were classified into chemical reaction driven gelation and physicochemical association driven gelation. The triggering mechanism involved in each process and the characteristics of each system are comparatively discussed. In addition, our perspectives on the in situ gelling systems are offered as signposts for the future advancement of this field.

Contents

Abbreviations: 3D, three dimensional; APS, ammonium persulfate; bFGF, basic fibroblast growth factor; CD, cyclodextrin; CMHA-S, thiol-modified carboxylmethyl hyaluronic acid; Con A, conconavalin A; DOPA, L-3,4-dihydroxyphenylalanine; ECM, extracellular matrix; GAG, glycosaminoglycan; GF, growth factor; GS, glutathione; GTN-DTPH, thiol-modified gelatin; HA, hyaluronic acid; HBP, heparin binding peptide; hGH, human growth hormone; HRP, horseradish peroxidase; LCST, lower critical solution temperature; LMWH, low molecular weight heparins; MMP, matrix metalloproteinase; MSC, meschenchymal stem cell; NIPAAm, N-isopropyl acryl amide; OPF, oligo[poly(ethylene glycol) fumarate]; PA, polyalanine; PAF, poly(alanine-co-phenylalanine); PAL, poly(alanine-co-leucine); PBS, phosphate buffered saline; PCL, polycaprolactone; PCLA, poly(caprolactone-co-lactic acid); PEG, poly(ethylene glycol); PLA, poly(lactic acid); PLGA, poly(lactic acid-co-glycolic acid); Pluronic®, poly(ethylene glycol)–poly(propylene glycol)–poly(ethylene glycol); P(PF-co-EG), poly(propylene fumarate-co-ethylene glycol); PP, phosphatase; PPG, poly(propylene glycol); QT, pentaerythriol tetrakis(3-mercaptopropionate); RGD, Arg-Aly-Asp; SELP, silk-elastin-like peptide; TEM, transmission electron microscopy; TEMED, N,N,N′N′-tetramethylethylene diamine; TG, transglutaminase; TGF, transforming growth factor; UV, ultraviolet; VEGF, vascular endothelial growth factor; VIS, visible.

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1. Introduction

A hydrogel is a three-dimensional (3D) network with high water content. It will neither disintegrate nor dissolve in an excess amount of water. Since the pioneering research dating back to 1960 [1], hydrogels have been extensively investigated [2–4]. In particular, in situ formed hydrogels have recently been recognized for their potential biomedical applications. Pharmaceutical agents or cells can be premixed as an aqueous solution (sol), followed by injection into a target site to form a hydrogel depot through a sol-to-gel transition mechanism. This provides a simple implantation method, without surgical procedures or complicate fabrication processes. The in situ formed gels have been investigated for their potential in various biomedical applications including minimally invasive drug delivery, 3D cell culture, injectable tissue engineering, surgical glues, tissue sealants, and adhesion prevention coating [5–7].

In this review, we summarize the recent progress on the in situ formed hydrogels. To make a hydrogel in situ, there should be a rapid pathway to form crosslinks that bind the highly swollen polymeric system in an excess amount of water. In considering the biomedical applications, the crosslinks should be generated in a biologically benign process. In this regard, the crosslinks generated by (1) chemical reaction driven processes such as redox/photo-polymerization, classical organic reactions, enzymatic reactions, and redox-reactions; and (2) physicochemical association driven processes such as thermogelation, ion-induced gelation, inclusion complex formation, stereocomplex formation, and complementary binding are discussed in this review (Fig. 1). In addition, our perspectives are offered and critical points that should be considered in designing a new in situ gelling system are suggested.

2. Chemical reaction driven gelation

In considering the biomedical applications of a hydrogel, a chemical reaction should not damage the biopharmaceuticals or cells. In this chapter, redox- or photopolymerization of acrylate-functionalized macromers; classical organic reactions including Michael addition and click reactions; enzymatic reactions using horseradish peroxidases (HRPs), transglutaminases (TGs), and phosphatases (PPs); and redox-reactions are discussed as in situ gel formation reactions. All these reactions are characterized as a chemical reaction driven gelation process because they involve new covalent bond formation or chemical changes during the gelation.

2.1. Redox/photo-polymerization

In considering biological application of an in situ gelling system, the gel forming reaction is recommended to occur in water, wherein the bioactive agents or cells are dissolved or suspended. In addition, polymerization involving high temperature or toxic heavy metals should be avoided. Therefore, redox-polymerization using a water soluble initiator and photo-polymerization that generates free radicals upon exposure to light have been developed for in situ gel formation. Synthetic hydrophilic macromers with acrylate/methacrylate groups were designed for redox/photo-polymerization. To provide biodegradability to the gel, a degradable block such as poly(lactic acid) (PLA) or polycaprolactone (PCL) was incorporated in the macromer. In addition, Arg-Gly-Asp (RGD) was incorporated in the gel to increase cell adhesion for 3D cell culture. In case of thermogelling macromers, combination of physical and chemical crosslinking systems was designed to improve the mechanical property of the physical gel (Fig. 2). Semisynthetic macromers originated