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Review

In situ forming hydrogels based on chitosan for drug delivery and tissue regeneration

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ABSTRACT

In situ forming hydrogels with simple sol–gel transition are more practicable as injectable hydrogels for drug delivery and tissue regeneration. State-of-the-art in situ gelling systems can easily and efficiently be formed by different mechanisms in situ. Chitosan is a kind of natural polysaccharide that is widely exploited for biomedical applications due to its good biocompatibility, low immunogenicity and specific biological activities. Chitosan-based in situ gelling systems have already gained much attention as smart biomaterials in the development of several biomedical applications, such as for drug delivery systems and regeneration medicine. Herein, we review the typical in situ gelling systems based on chitosan and mechanisms involved in hydrogel forming, and report advances of chitosan-based in situ gels for the applications in drug delivery and tissue regeneration. Finally, development prospects of in situ forming hydrogels based on chitosan are also discussed in brief.

1. Introduction

Hydrogels are the polymeric materials with three dimensional networks, which have gained much attention in biomedical fields as carriers for drugs, protein, cells, and others because of their good biocompatibility, solute permeability and tunable release characteristics [1]. The retaining ability of a large amount of water within their structures which results in high water content and soft-surface properties is the character that makes them compromised on the surrounding tissues and leads to a good biocompatibility. Since the development of hydrogels in 1960s, numerous studies on adapting hydrogels as biomaterials have been reported. Especially, the in situ forming hydrogels which usually show sol-to-gel transition at the in-situ site where they are administrated into the body, exhibit promising potentials for clinic applications. It is more practicable to apply in-situ forming hydrogels to tropical drug delivery, injectable implant, tissue engineering scaffold and so on [2–5]. The drug/cell can be mixed with the aqueous sol for convenient administration

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like injection and then a gel depot encapsulating drug/cells is formed in situ. In situ gelling systems could potentially alleviate several drawbacks associated with contemporary regenerative medicine approaches and scaffolds. Primarily, they minimize the invasiveness of the open surgical technique and can conform to complex 3D geometries, which is critical in implant drug delivery system, repair of trauma, and regeneration post-tumor resection. More importantly, this allows for delivery of cells and growth factors locally, which could potentially lead to faster and complete regeneration [6].

Chitosan, the second most abundant natural polysaccharides next to cellulose, has many advantages over other polymers, like nontoxicity, biocompability and biodegradability. Chitosan is a family of cationic polysaccharides with a basic chemical structure of (1,4)-linked 2-amino-2-deoxy-D-glucans, which are produced commercially by the partial deacetylation of chitin obtained from the reprocessing of seafood waste. Members of the chitosan family differ in terms of their molecular weight and degree of deacetylation. Chitosan is biodegradable, as it is broken down in the human system to harmless products (amino sugars) that can be easily absorbed. Nowadays, chitosan and its derivates have been investigated for many diverse medical applications, such as wound dressings, contact lenses, and materials for cell encapsulation, drug delivery and so on [7–9]. Additionally, chitosan has several active functional groups that allow for protein binding and an inherent positive charge that is known to stimulate cell interactions and differentiation.

By far, chitosan-based hydrogels have proven to be very efficient for the delivery of biologically active molecules like insulin, growth factors, and for providing organization of cells and tissues, due to the possibility to create multilayered system [10]. There are also many reports about chitosan-based in situ hydrogels that can be delivered in minimally invasive techniques such as injection, ocular or nasal administration while protecting drugs or cells from the hostile environment. In this paper, several typical in situ gelling systems based on chitosan are reviewed together with their biomedical applications in drug delivery and tissue regeneration.

2. Mechanisms to generate in situ hydrogels

A gel is defined as a three-dimensional network swollen by a solvent. Hydrogels are hydrophilic polymeric networks able to absorb and retain high quantities of water while retaining its shape. Based on how the network is connected, hydrogels can be classified into two categories: the chemical hydrogels where the hydrophilic polymer chains are associated together by covalent bonds, and the physical hydrogels by secondary forces, such as hydrogen bonds, ionic bonds, intermolecular hydrophobic association and so on. Mechanisms involved in in situ gel formation may include the following: gelation in response to temperature or pH change, ionic or covalent cross-linking, solvent exchange or crystallization, or simply thickening upon removal of the injection shear.

Among them, thermoresponsive gelling polymers [11,12] are included with unique characters, which usually exhibit phase change behaviors of sol-to-gel or gel-to-sol transition upon an increase in temperature, and have gained enormous attention to form in situ gels with promising biomedical applications. Commercially available block copolymers of poly(ethylene oxide-b-propylene oxide-b-ethylene oxide) (PEO-PPO-PEO) are the best-known examples of thermally gelling polymers. Aqueous solutions of PEO-PPO-PEO copolymers demonstrate phase transitions from sol to gel (low temperature sol-gel boundary) and gel to sol(high temperature gel-sol boundary) with monotonically increasing temperature when the polymer concentration is above a critical value. Moreover, biodegradable copolymers of polyethylene glycol and poly(lactic/glycolic acid) such as PLGA-PEG-PLGA, PEG-PLGA-PEG, mPEG-b-PCL and so on, were recently developed also with thermal-responsive sol-to-gel transition [13–16]. Aqueous solutions of these copolymers form soft gels at body temperature (37 °C) but flow freely at room temperature. Therefore, subcutaneous injection of the copolymer formulation resulted in an in situ-forming gel that exhibited controlled drug release. Formulations are water based, easy to sterilize by simple filtration of the aqueous solution. Ideally, the duration of the gel should be matched with its function as a temporary tissue scaffold or a drug release depot. By optimizing the composition of copolymers, injectable scaffolds with a broad range of gel degradation time can be designed.

Besides the classic systems mentioned above, enzymatically cross-linked hydrogels [17] have emerged recently as in-situ gelling system with increasing interest, which can be formed by enzyme-catalyzed mild-cross-linking reactions in situ. Hydrogels prepared by using enzyme systems like tyrosinases, transferases and lysyl oxidases show interesting characteristics as dynamic scaffolds and as systems for controlled release. Additionally, unwanted side effects can be avoided because of the substrate specificity of the enzyme. In situ cross-linkable gels are based on aqueous mixtures of gel precursors with bioactive agents that can be administrated via a syringe. Moreover, injectable enzymatically cross-linked hydrogels offer a plausible solution for the generation of functional tissue substitutes of these gels and native tissue, therefore maintaining the cell phenotype, which is highly relevant for tissues like cartilage. Importantly, the poor or limited mechanical properties of some hydrogels can be improved by combining enzyme types such as transglutaminases and horseradish peroxidases systems, after adjusting the material design. For example, transglutaminases are highly interesting as they offer intimate integration between the in situ formed gel and the native host tissue. Engineered peroxidases with higher stability and catalytic efficiency are currently being developed. In the near future, further applications using this enzyme type will be developed and continue to prosper in the tissue engineering field.

3. Typical in situ gelling systems based on chitosan

According to the mechanism of gel formation, chitosan-based in-situ gelling systems can be classified into two categories: in-situ covalent cross-linking system and in-situ phase separation system.