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Review

New progress and prospects: The application of nanogel in drug delivery

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ABSTRACT

Nanogel has attracted considerable attention as one of the most versatile drug delivery systems especially for site-specific and/or time-controlled delivery of bioactive agents owing to their combining features of hydrogel and nanoparticle. Physically synthesized nanogels can offer a platform to encapsulate various types of bioactive compounds, particularly hydrophobic drugs and biomacromolecules, but they have poor mechanical stability, whereas nanogels prepared by chemical cross-link have a wider application and larger flexibility. As an ideal drug-delivery carrier, nanogel has excellent drug loading capacity, high stability, biologic consistence and response to a wide variety of environmental stimuli. Nowadays, targeting and response especially multi-response of the nanogel system for drug delivery have become an issue in research. And the application study of nanogels mainly focuses on antitumor agents and proteins. This review focuses on the formation of nanogels (physical and chemical cross-linking) and their release behavior. Recent application of nanogels is also discussed.

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1. Introduction

In recent years, nanotechnology has been widely applied in drug delivery system since it offers a suitable method for site-specific and/or time-controlled delivery of bioactive agents. The nanoscale size gives these delivery systems a lot of advantages, especially on improving solubility of hydrophobic drugs, increasing drug accumulation in tumors, enhancing the stability of therapeutic agents against chemical/enzymatic degradation, and decreasing cytotoxic side effects. Several types of nanoscale delivery systems have been reported, including polymeric micelle, liposome, sol–gel and so on [1–3]. Since the hydrogel was found, numerous efforts and studies have been devoted to expanding

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its application, especially in pharmaceutical and biomedical areas. Gel can be considered as a soft material which combines the properties of solids and fluids. Their biocompatibility is attributed to the high water content and low surface tension, while the porosity contributes to high loading capacity and the swelling property makes controlled release possible.

By definition, nanogels are sub-micron size three-dimensionally cross-linked polymer networks. Nanogel is composed of hydrogel particulate entities with a nanometer sized space, so it has the features of hydrogel and nanoparticle mentioned above at the same time. According to the material, nanoparticles generally include lipid nanoparticles, inorganic nanoparticles and polymer nanoparticles. Obviously, the nanogels belong to the last type. Nanogels can be prepared from polymer precursors or prepared via heterogeneous polymerization of monomers. The key point of fabricating nanogels is cross-link, including physical cross-link and chemical cross-link. Nanogels have the ability of absorbing high amounts of water or biological fluids while maintaining their structure, which is attributed to the presence of hydrophilic groups such as –OH, –CONH–, $–CONH_2–$, and $–SO_3H$ in the polymer [4]. However, nanogels show swelling property instead of being dissolved because of the existence of cross-links in the nanogels. This unique property makes nanogel a promising candidate for a lot of applications. Numerous studies show that nanogel is an ideal drug-delivery carrier due to its excellent drug loading capacity, high stability, biologic consistence and response to a wide variety of environmental stimuli (such as ionic strength, pH, and temperature) that are unprecedented for common pharmaceutical nanocarriers [5,6].

2. The mechanism of forming nanogel

As mentioned above, swelling is the most important feature of nanogel, which is achieved by chemical or physical cross-link between polymers. In other words, the essence of forming nanogels is to form suitable cross-links between polymers [7]. Representative and commonly used cross-links are talked in this section.

According to the feature of materials used in forming nanogels, the methods to prepare nanogels can be divided into two major categories: 1) fabricating nanogels from polymer precursors; and 2) preparing nanogels via heterogeneous polymerization of monomers. Polymer precursors are polymers such as amphiphilic or triblock copolymers which can form nanogels by self-assembly or polymers that have a number of reactive sites which can be directly used for chemical cross-linking. Of course, polymers can also be modified with groups which can be subsequently used to form physical or chemical cross-links [8]. The preparation of nanogels via monomer polymerization includes two steps, polymerization and formation of nanogels, which are usually accomplished simultaneously. Compared with preparation of nanogels using preformed polymers, synthesizing nanogels via monomer polymerization exhibits higher efficiency. These two approaches are illustrated in Fig. 1. Physical cross-linking usually occurs between polymer precursors with special nature, while chemical cross-linking can be formed with both polymer precursors and monomers.

2.1. Physical interactions

Physical interactions between the polymers can be divided into two categories: Van der Waals force (mainly includes hydrogen bond and hydrophobic interaction) and electrostatic interaction. Nanogels formed by physical interactions between polymer chains can offer a platform to encapsulate various types of bioactive compounds, especially hydrophobic drugs and biomacromolecules. And the preparation of physically cross-linked nanogels usually occurs in aqueous media and mild conditions. The environmental parameters, such as the pH value, ionic strength, and temperature should be controlled strictly, since they have a great influence on the particle size. Of course, the topmost priority is the structure of the polymers such as the block nature, block lengths and so on [9].

2.1.1. Amphiphilic-association

As we all know, amphiphilic polymers can self-assemble into micelles with core–shell structure in appropriate conditions. The

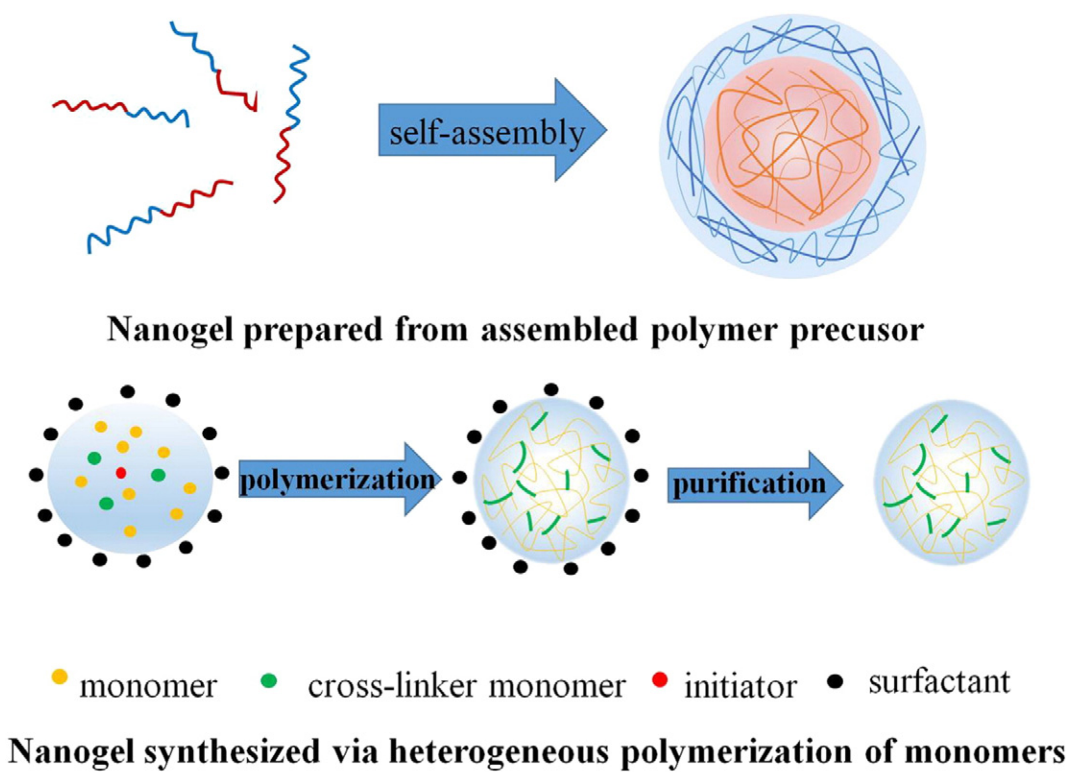

Fig. 1. The methods of nanogels synthesis: polymer precursor method and heterogeneous monomer polymerization method.