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Review

Electroconductive natural polymer-based hydrogels

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ABSTRACT

Hydrogels prepared from natural polymers have received immense considerations over the past decade due to their safe nature, biocompatibility, hydrophilic properties, and biodegradable nature. More recently, when treated with electroactive materials, these hydrogels were endowed with high electrical conductivity, electrochemical redox properties, and electromechanical properties; consequently, forming a smart hydrogel. The biological properties of these smart hydrogels, classified as electroconductive hydrogels, can be combined with electronics. Thus, they are considered as good candidates for some potential uses, which include bioconductors, biosensors, electro-stimulated drug delivery systems, as well as neuron-, muscle-, and skin-tissue engineering. However, there is lacking comprehensive information on the current state of these electroconductive hydrogels which complicates our understanding of this new type of biomaterials as well as their potential applications. Hence, this review provides a summary on the current development of electroconductive natural polymer-based hydrogels (ENPHs). We have introduced various types of ENPHs, with a brief description of their advantages and shortcomings. In addition, emerging technologies regarding their synthesis developed during the past decade are discussed. Finally, two attractive potential applications of ENPHs, cell culture and biomedical devices, are reviewed, along with their current challenges.

1. Introduction

Several natural hydrophilic polymers including polysaccharides (e.g. hyaluronic acid, alginate, chitosan, and cellulose), proteins (collagen, gelatin), and DNA etc. form a three-dimensional (3D) network that can retain a large amount of interstitial water, hence forming a naturally derived hydrogel. These hydrogels can be utilized for various potential biomedical applications due to their high biocompatible nature. Nonetheless, they have obvious shortcomings associated with them, for example; unsatisfactory mechanical properties, difficulty in controlling their degradation and structure due to their fabrication method, and potential immunogenicity, which limits their applicability for more extensive uses [1]. However, researchers around the world made some significant contributions with regard to methods of synthesis, fabrication, and modification of natural hydrogels in a desired way, which could possibly be used to eliminate these limitations in the future. Thus, naturally derived hydrogels that are similar to native extracellular matrices (ECMs), with a fine 3D network, high water content, good biocompatibility, and versatile fabrication methods, have emerged as promising matrices for the fabrication of electroconductive hydrogels. Hydrogels can be endowed with electrical properties via blending, doping, or chemical modification with electroactive materials. For example, in doping, the electroconductive behavior of these hydrogels is due to the charge transfer in the polymer matrix either by n-type (reduction) or p-type (oxidation), which results in the creation of unbound charge carriers [2]. The conductivity of these electroactive hydrogels is dependent on the dopant, its type, and efficiency to abstract or induce an electron within the matrix [3]. Furthermore, the conductivity also depends on the mobility of

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charge carriers that could occur intra- or inter-chain [2]. In addition, the electronic and ionic transporting abilities of hydrogels could be enhanced if they were fabricated into materials with large surface areas and porous microstructures. The mechanical properties of electroconductive hydrogels can be optimized using various synthetic methods and processes, which could significantly broaden their applications. Their better biocompatibility minimizes the toxicity of the electroactive materials, and therefore, they could possibly be exposed to the natural environment of a human body. In particular, the cell-signaling and cell-interactive properties of natural polymers [4] could be coupled with electrical stimulation and used in neuron-, muscular-, and skin-tissue engineering.

Recently, several excellent reviews have been published that focus on the biofabrication of hydrogels [5], their design and applications in cell cultures [6], and their use in regenerative medicine [1]. In addition, many functional and smart hydrogels, such as electroconductive hydrogels based on synthetic hydrogels, have been designed and subsequently fabricated [7,8]. However, there is lacking a compilation of comprehensive information on the current state of such natural polymer-based electroconductive hydrogels. Hence, this work provides a summary and conclusion on the current development of electroconductive natural polymer-based hydrogels (ENPHs) with regard to their fabrication and key biomedical applications.

2. Natural polymer-based hydrogels

Hydrogels can generally be considered as polymeric materials that retain a large amount of water (free/freezable or bound/non-freezable water) and offer good inherent biocompatibility. These contain two phases, a solid and a liquid phase. The solid phase of the hydrogels consists of a three-dimensional (3D) polymeric network derived from extremely hydrophilic monomers, which are ultimately turned into insoluble materials as a result of cross-linking. Due to this solid phase, the hydrogels can acquire good soft elastomeric mechanical properties when liquid phase, for example water is incorporated into their network [9]. Additionally, the shape and size of the hydrogels can easily change in response to external stimuli that involve the expulsion or absorption of free water. Further, the water can carry the reactive, monomeric, and potentially polymerizable species into the interstices of the hydrogel matrix and occupies the empty spaces. These also interact with the chain segments or pendant moieties of the hydrogel matrix [10]. In the absence of water, it is possible that the fibrous network of the hydrogels may not exhibit the same properties.

Natural polymer-based hydrogels are of substantial interest in various research fields due to their highly safety level and unique properties, such as high biocompatibility, biodegradability, and hydrophilic nature. To date, various types of natural polymer-based hydrogels have been synthesized, such as polysaccharide-based hydrogels (HA, alginate, chitosan, and cellulose), protein-based hydrogels (collagen, gelatin), and DNA-based hydrogels (Fig. 1). The following section briefly describes these hydrogels.

2.1. Hyaluronic acid-based hydrogels

Hyaluronic acid (HA) is a non-sulfated glycosaminoglycan that contains the alternating units of D-glucuronic acid and D-*N*-acetylglucosamine which are linked via alternating β-1,4 and β-1,3-glycosidic bonds [11]. Naturally, HA exists in the form of a straight-chain anionic polysaccharide and is extensively dispersed throughout the human body. Under mild conditions, it can be physically cross-linked by freeze–thaw techniques, without the use of organic solvents or toxic cross-linking agents [12]. In addition, HA can be easily modified owing to the functional carboxylic acid-, hydroxyl-, and *N*-acetyl groups that are present within its structure.

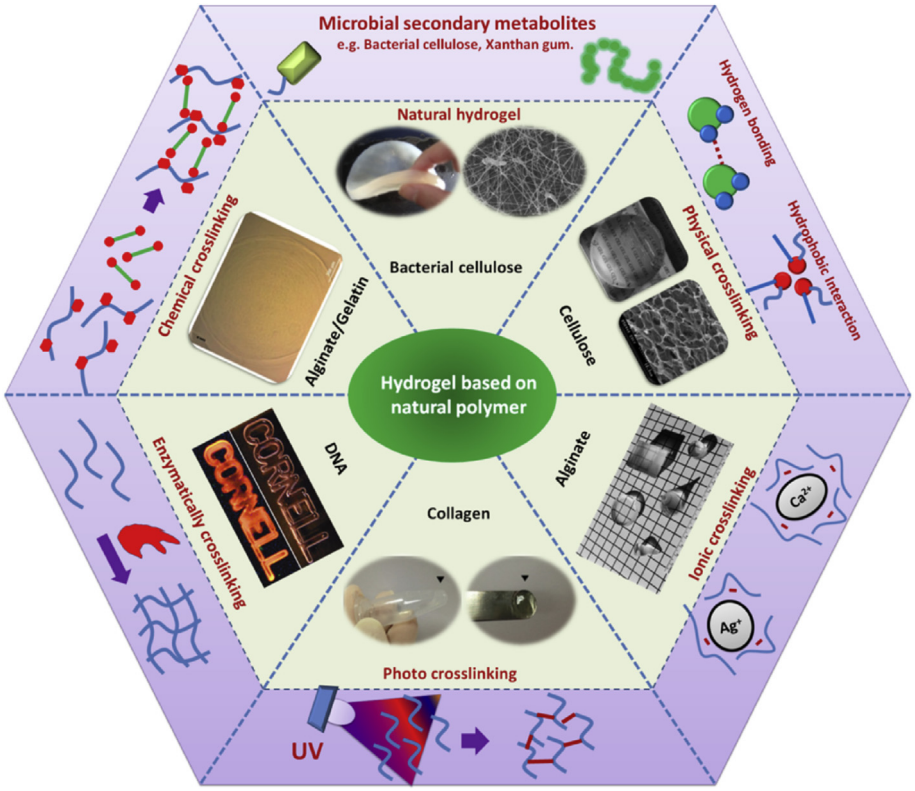

Fig. 1. Various types of natural polymer-based hydrogel. Reproduced with permission from Refs. [33,55–59].