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Physically crosslinked hydrogels from polysaccharides prepared by freeze–thaw technique

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ABSTRACT

Natural polysaccharides are abundant, inexpensive, renewable, modifiable and have biodegradable and biocompatible characteristics. Polysaccharides offer a very promising source for materials of tomorrow. This review addresses recent progress in polysaccharide-based cryogels, one kind of novel physical hydrogels prepared by freeze–thaw technique under mild conditions and in the absence of organic solvents and toxically crosslinking agents. Polysaccharides used to fabricate physical cryogels here are, hyaluronan, carboxymethylated curdlan, carboxymethylated cellulose, xanthan, β-glucan, locust bean gum, starch (amylose, amylopectin and their mixtures), maltodextrins and agarose. Composite cryogels of based on polysaccharides and polyvinyl alcohol are also introduced. Various physically crosslinked cryogels from polysaccharides with tunable structural, mechanical, biological properties as well as multiple applications are considered and the investigations of the formation mechanism for these cryogels are also addressed.

1. Introduction

The term hydrogel describes three-dimensional network structures obtained from a class of synthetic and/or natural polymers which can absorb and retain significant amount of water or biological fluids [1–3]. The hydrogel structure is created by the hydrophilic groups or domains present in a polymeric network upon the hydration in an aqueous environment. There has been increasing interest in biopolymer hydrogels due to their inherently desirable biocompatibility and degradability, environmentally friendly characteristics and bioactivities. Hydrogels have wide potential applications in the fields of food, biomaterials, agriculture, water purification, etc. Recently, intense effects are devoted to developing novel hydrogels for applications as biomaterials for drug delivery [4,5], tissue engineering [6,7] sensors [8], purification [9,10], wound dressing [11,12] and catalyst [13].

On basis of the manners of crosslinking among the macromolecules in hydrogels, two main categories can be classified by whether the crosslinking is chemically or physically based [14,15]. Chemical crosslinking is assuredly a highly versatile method to create hydrogels with satisfying and tailored mechanical performances [16]. However, the crosslinking agents used are often toxic compounds, which have to be extracted from the gels before used. Moreover, crosslinking agents can give unwanted reactions with the bioactive substances present in the hydrogel matrix. The use of crosslinking agent or the existence of reacting byproducts in final hydrogels cannot be totally avoided in the process of synthesizing hydrogels by chemical reaction. These will impair the biocompatibility and endow the hydrogels with risk in both short and long-term applications, especially in biomedical aspects [17].

Such adverse effects are avoided with the use of physically crosslinked gels. Physical hydrogels, especially some based on natural biopolymers are good alternatives and are thought to be promising materials with hugely potential applications in biomedical field because the gel formation can be often carried out under mild conditions and in the absence of organic solvents and toxically crosslinking agents [18]. One of these hydrogels with considerable potential of biomaterials is physical cryogel prepared by freeze–thaw technique, especially the gel based on polysaccharides, due to their well documented biocompatibility, low or non-toxicity and degradability under physiological conditions either enzymatically or chemically [19–21]. This paper reviewed the recent developments on polysaccharide-based novel physical cryogels with emphasis on their fabrication, property and gelation mechanism.

2. General introduction to polymeric cryogels

The cryogels result from cryogelation or cryostructuring that a specific type of gelation that occurs upon cryogenic treatment of the initial solution or dispersions potentially capable of forming a gel [20]. The polymeric cryogels are macroporous heterophase gels

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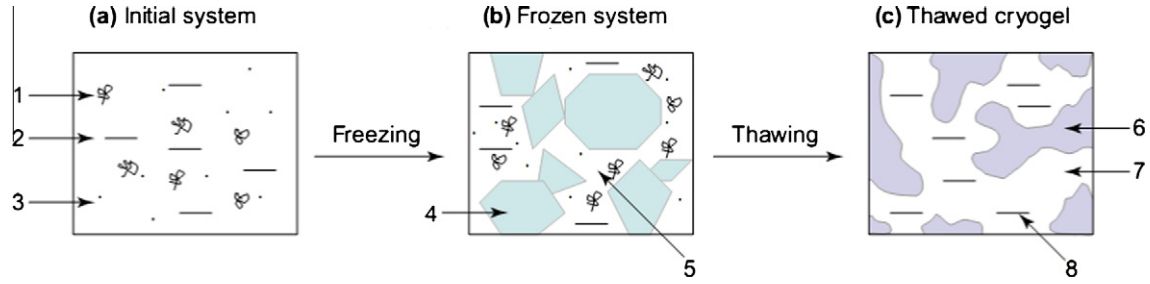

Fig. 1. The main process of formation of the polymeric cryogel: 1, macromolecules in a solution; 2, solvent; 3, low-molecular solutes; 4, polycrystals of frozen solvent; 5, unfrozen liquid microphase; 6, polymeric framework of a cryogel; 7, macropores; 8, solvent [22].

formed as a result of the freezing, storage in the frozen state, and subsequent thawing of the initial solutions or dispersions in which preconditions for structure formation and transition into a gel are already present or are specially created [22]. An obligatory condition for the formation of heterogeneous gels is then the crystallization (freezing) of the main bulk of the solvent. After thawing out, cryogels, or cryostructurates are formed [23]. Forced alignment of polymeric chains as the polymer concentration is increased by conversion of water to ice may provide a mechanism for the formation of side-by-side associations, which then remain intact on thawing, as the junction zones of the gel. The formation of cryogels is schematically presented in Fig. 1.

The scope of applications of the cryotropic gelation techniques and the gel materials is fairly broad. The unique porous structure of polymeric cryogels proves to be useful in many cases. A large number of publications [20,23–29] have been devoted to the use of various cryogels as materials for biomedical and biotechnological purposes.

3. Physical cryogels based on various polysaccharides

There has been an increased interest in physical gels due to the relative ease of production and the advantage of not using chemically crosslinking agents [17]. Physical cryogels based on polysaccharides, which are produced by freeze–thaw of polysaccharide solutions, inherently have additional advantages of being biocompatible, biodegradable and eco-friendly. Therefore, study on the physical cryogels based on polysaccharides currently is an area receiving considerable attention both theoretical and applied. By varying the kinds of polysaccharides, the nature of soluble additives, and also the regime in the cryogenic treatment (temperature and duration of freezing, rate of thawing, the number of refreezing cycles, etc.), it is possible to regulate and modulate the properties of the final gels and their macro- and micro-structures. Actually quite a lot of polysaccharides such as hyaluronan (HA), carboxymethylated curdlan (CMc), carboxymethylated cellulose (CMC), xanthan, β-glucan, locust bean gum (LBG), starch (amylose, amylopectin and their mixtures), maltodextrins (MDs) and agarose are capable of forming cryotropic gels. Generally, the degree of gelation or the stability and mechanical performance of the gel formed depends on pH, temperature for freezing, time of freezing period and cycles of freeze–thaw, and the stability and mechanical properties of cryogels are usually increasing with increasing the freezing time and freeze–thaw cycles.

3.1. Various polysaccharide cryogles

HA is one of the most important and ubiquitous glycosaminoglycan in vertebrate bodies with unbranched molecular chain composed of a repeating disaccharide unit of D-glucuronic acid (GlcUA) and N-acetyl-D-glucosamine (GlcNAc) [30,31]. Although it is known that HA is a kind of non-gelling polysaccharide, cryotropic gels and viscoelastic putty gels of unmodified HA are found to be able to form under certain conditions. The viscoelastic putty gel can be obtained by adjusting the pH of the concentrated HA solution to 2.5 at physiological ionic strength [32]. But such a putty gel is unstable, and it will convert to the solution state again after adjusting the pH below 2.0 or above 3.0. Therefore, this severe limitation of putty gel prevents its application. The cryotropic gel of HA, produced by once or repeating freeze–thaw, was firstly reported by Okamoto et al. [33]. This kind of gel overcame the drawbacks of putty gel due to its stronger stability under different pH or temperature conditions. The main procedures of the preparation of HA cryogels include acidifying HA solution and then freeze–thaw of the acid HA solution at proper subzero temperature by once or repeating freeze–thaw. Fig. 2 showed the appearance of a kind of HA formless cryogel [34,35]. Experimental results indicated that this HA weak gel showing a thermoreversible property was constructed by entangled bundle-like structures that could be melted at elevated temperature above 70 °C [34,35].

Curdlan is a naturally occurring linear polysaccharide entirely composed of 1,3-β-D-glucosidic linkages [36]. This kind of glucan shows strong bioactivities and is capable of forming physical hydrogels by various methods [37–39]. CMc is the carboxymethylation derivative of curdlan with good water solubility bioactivity as well [40,41]. Similar to HA, CMc aqueous solutions can form physically crosslinked gels at low pH values by freezing (Fig. 2). The pH has a significant influence on the gelation of CMc. 1% CMc solutions at pH below 2.40 can form gels whereas solutions at pH of 2.94 cannot form gels. The densification and subsequent stiffness of the hydrogels become strong and the equilibrium swelling ratios of CMc gels decrease with increasing the number of freeze–thaw cycles or lowering the pH values [42]. The formed CMc cryogels can persist even when the heating temperature keeps at 70 °C for 20 h. In addition, interestingly, it is also found that CMC at a low concentration (1%) with the same feature of having carboxylic groups can also form hydrogels at low pH by freezing [42].

Xanthan gum is an anionic polysaccharide produced commercially by bacterial fermentation. It is composed of the sugars glucose, mannose, and glucuronic acid. The backbone is similar to cellulose, with added side chains of trisaccharides. Xanthan cryogel can be formed by directly freeze–thaw treatment, the process of which is more convenient than that of HA or CMc cryogel in which the acidifying solution is indispensible [43]. The mechanical properties of xanthan cryogel are determined by many process parameters such as freezing time, freeze–thaw cycles and freezing temperature, similar to most of cryogels. However, the concentration-dependence of gel moduli for the xanthan cryogels is unusual, with storage modulus G' reaching a maximum value but then decreasing slightly at higher concentrations as shown in Fig. 3. Addition of sugars (sucrose, glucose, fructose, maltose) at concentrations up to 10 wt% has no effect on the strength of the cryogels, but higher concentrations cause a progressive reduction in moduli,