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Review

Carrageenan and its applications in drug delivery

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ABSTRACT

Carrageenan is a sulphated linear polysaccharide of D-galactose and 3, 6-anhydro-D-galactose obtained by extraction of certain red seaweeds of the Rhodophyceae class. The objective of this review is to summarize recent applications of carrageenan in drug delivery systems. So far, carrageenan has been investigated as an excipient in pharmaceutical industry, for example, as polymer matrix in oral extended-release tablets, as a novel extrusion aid for the production of pellets and as a carrier/stabilizer in micro/nanoparticles systems. Moreover, based on the special characteristics of carrageenan such as the strong negative charge and gelling, it has been used as a gelling agent/viscosity enhancing agent for controlled drug release and prolonged retention. Furthermore, carrageenan has been used for tissue regeneration with therapeutic biomacromolecules and for cell delivery. Other potential applications and safety evaluation of carrageenan are still to be undertaken in the near future.

Contents

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1. Introduction

Polysaccharides are being widely utilized for drug delivery (Coviello, Matricardi, Marianecci, & Alhaique, 2007). In recent years, marine microorganisms such as bacteria, microalgae and seaweeds, have represented a largely untapped reservoir of valuable materials. Among them, seaweeds are the most abundant sources of polysaccharides such as carrageenan, alginate and agar (De Ruiter & Rudolph, 1997; Jiao, Yu, Zhang, & Ewart, 2011; Michel, Nyval-Collen, Barbeyron, Czjzek, & Helbert, 2006).

Carrageenan (CG) is the generic name for a family of high molecular weight sulphated polysaccharides obtained by extraction of certain species of red seaweeds. It is composed of galactose and anhydrogalactose units linked by glycosidic unions (Coviello et al., 2007; Jiao et al., 2011). In food industry, CG is widely utilized due to its excellent physical functional properties, such as gelling, thickening, emulsifying and stabilizing abilities, and has been employed to improve the texture of cottage cheese, puddings and dairy desserts, and as binders and stabilizers in the meat processing industry for the manufacture of sausages, patties and low-fat hamburgers (Campo, Kawano, Silva, & Carvalho, 2009; Chen, Yan, Wang, Xu, & Zhang, 2010; Kavitha, Mohan, Satla, & Gaikwad, 2011). In addition to industrial food applications, CG is also used in toothpaste, air freshener gels, fire fighting foam, cosmetic creams, shampoo and shoe polish (Necas & Bartosikova, 2013). In recent years, it is increasingly used in pharmaceutical formulations. At present, CG has already been included in United States Pharmacopeia 35-National Formulary 30 S1 (USP35-NF30 S1), British Pharmacopoeia 2012 (BP2012) and European Pharmacopoeia 7.0 (EP7.0), implying that CG may have a promising future as a pharmaceutical excipient. However, compared with commonly used pharmaceutical excipients such as hydroxypropyl methylcellulose (HPMC), chitosan (CS), carbomer and alginate, the utilization of CG in the discipline of pharmaceutics is not frequently reported. And, only limited reviews are available about the evaluations of CG in pharmaceutical industry (Bhardwaj, Kanwar, Lal, & Gupta, 2000; Campo et al., 2009; De Ruiter & Rudolph, 1997; Liang, 2009; Rinaudo, 2008). Systemic reviews about the various applications of CG in drug delivery are still absent so far to the best of our knowledge. Therefore, the objective of this paper is to present a comprehensive overview of properties of CG and its applications in various drug delivery systems.

2. General properties of carrageenan

2.1. Sources and production of carrageenan

The main species of seaweed from which CG is manufactured are *Chondrus, Eucheuma, Gigartina, and Hypnea*. Specific details of extraction processes are regarded as trade secrets by the several manufacturers of CG, but broadly these follow a similar pattern. The seaweed is dried quickly to prevent degradation, and is then baled for shipment to processing facilities. The seaweed is repeatedly washed to remove gross impurities such as sand, salt, and marine life, and then undergoes a hot alkali extraction process, releasing the CG from the cell. Once CG is in a hot solution, it undergoes clarification and then is converted to powder (Rowe, Sheskey, & Quinn, 2009). Meanwhile, extraction parameters (such as temperature, pH, duration) and alkaline pre-treatment duration have important effects on the chemical structure and gelling properties (Hilliou et al., 2006).

In general, several methods have been used to remove CG from solution. The first method is “freeze–thaw” technique. The solution is gelled with various salts, then the gels are frozen. Upon thawing, water is removed and the resultant mass, primarily CG and its salt, is ground to the desired particle size. The second method, referred to as “alcohol precipitation method”, is to place the concentrated solution of CG in 2-propanol or other alcohols, leading to CG precipitation out of solution. The solvents are then evaporated and the precipitated CG is dried and ground to the desired particle size. The third method is “KCl precipitation” process, where after hot extraction, the filtrate is evaporated to reduce the volume. The filtrate is then extruded through spinnerets into a cold 1.0–1.5% solution of KCl. The resulting gel threads are further washed with KCl solution and are pressed, dried and milled to CG powder (McHugh, 1987; Rowe et al., 2009). The economics of extraction processes is strongly affected by the cost of the energy required to bring the CG into solution and subsequently recover it in dry form (McHugh, 1987).

Commercial CG is usually standardized by blending different batches of CG and adding salt or sugar to obtain the desired gelling or thickening properties (MarcelTradingCorporation, 2013). So far, the main commercial sources of CGs are κ-CG (Gelcarin® GP-812NF, Gelcarin® GP-911NF), τ-CG (Gelcarin® GP-379NF, SeaSpen® PF), and λ-CG (Viscarin® GP-109NF, Viscarin® GP-209NF).

2.2. Chemical structure and physicochemical properties of carrageenan

CGs are mainly obtained from different species of Rhodophyta: *Chondrus, Eucheuma, Gigartina*, and *Hypnea* (Campo et al., 2009; Jiao et al., 2011). They are mainly composed of D-galactose residues linked alternately in 3-linked-β-D-galactopyranose and 4-linked-α-D-galactopyranose units and are classified according to the degree of substitution that occurs on their free hydroxyl groups. Substitutions are generally either the addition of ester sulfate or the presence of the 3, 6-anhydride on the 4-linked residue (Campo et al., 2009; Nanaki, Karavas, Kalantzi, & Bikiaris, 2010). In addition to D-galactose and 3,6-anhydro-D-galactose as the main sugar residues and sulphate as the main substituent, other carbohydrate residues may present in CG preparations, such as glucose, xylose and uronic acids, as well as some substituents, such as methyl ethers and pyruvate groups (Campo et al., 2009; De Ruiter & Rudolph, 1997). These polysaccharides can also be traditionally split into six basic forms: Kappa (κ)-, Iota (τ)-, Lambda (λ)-, Mu (μ)-, Nu (ν)- and Theta (θ)-CG. This nomenclature is relevant to their chemical structures and commercial production, since different CG subtypes are extracted from distinct weed sources (Campo et al., 2009; Knutsen, Myslabodski, Larsen, & Usov, 1994). The primary differences which influence the properties of CG type are the number and position of ester sulfate groups as well as the content of 3,6-anhydro-galactose (3,6-AG). For instance, it was reported that higher levels of ester sulfate resulted in lower solubility temperature and lower gel strength (Necas & Bartosikova, 2013). Three most important types of CGs (important from commercial point of view) are kappa (κ), iota (τ) and lambda (λ), and their structures are presented in Fig. 1 (Sankalia, Mashru, Sankalia, & Sutariya, 2006a). As can be seen from their chemical structures, 3, 6-anhydrobridges are present in κ- and τ-CG but not in λ-CG. The κ-, τ-, and λ-CG dimers have one, two and three sulphate ester groups, resulting in calculated sulphate content of approximately 20%, 33% and 41% (w/w), respectively (De Ruiter & Rudolph, 1997; Nanaki et al., 2010). Typically, commercial κ-CG contains approximately 25% ester sulfate and 34% 3,6-AG; τ-CG contains approximately 32% ester sulfate and 30% 3,6-AG; λ-CG contains approximately 35% ester sulfate and little or no 3,6-AG (FMCBioPolymer, 2013a). In summary, three types of CGs have similar characteristics in chemical structure. NMR spectroscopy (^{1}H NMR or ^{13}C NMR spectroscopy), colorimetric and chromatographic methods can be used for structural analysis of CGs (Campo et al., 2009). In addition, fourier transform infrared spectroscopy and multivariate regression can also be utilized for