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Review

Carrageenan and its applications in drug delivery

Liang Li, Rui Ni, Yang Shao, Shirui Mao*

School of Pharmacy, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang 110016, China

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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

* Corresponding author. Tel.: +86 24 23986358; fax: +86 24 23986358.
E-mail addresses: maoshirui@syphu.edu.cn, maoshirui@vip.sina.com (S. Mao).

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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

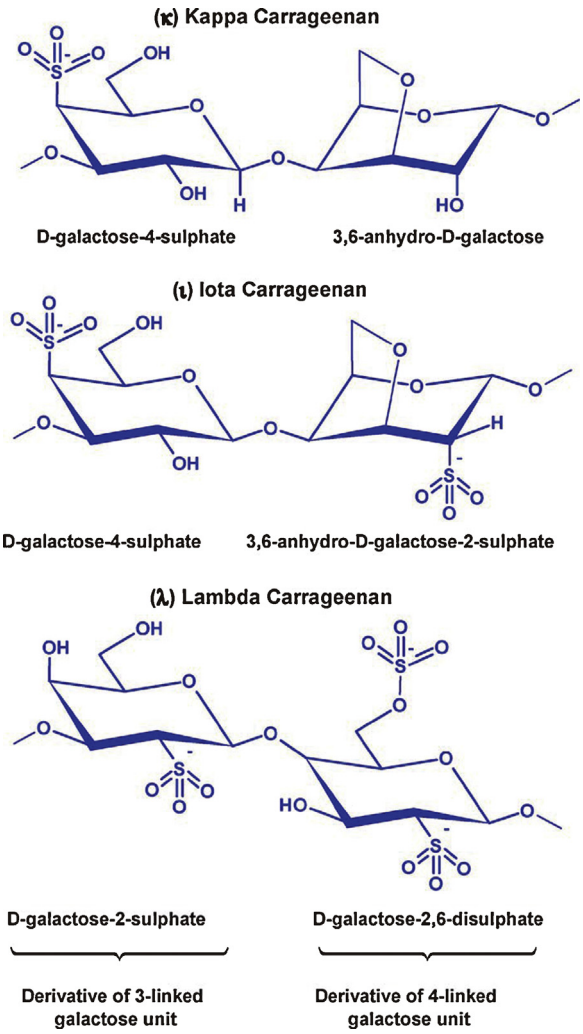

Fig. 1. Schematic representation of idealized repeating units of carrageenans. Reprinted from Ref. (Sankalia et al., 2006a), Copyright (2006), with permission from Elsevier.

quantitative determination of CGs in industrial mixtures (Prado-Fernandez, Rodriguez-Vazquez, Tojo, & Andrade, 2003; Volery, Besson, & Schaffer-Lequart, 2004).

Commercial CGs have an average molecular weight ranging from 100 to 1000 kDa. Table 1 shows some basic properties of commercial CGs (FMCBioPolymer, 2013b). The pK_a value of the anionic sulfate groups on CGs is around 2, which determines the degree of ionization in different media (Gu, Decker, & McClements, 2004b). κ- and τ-CG are known to undergo a thermally-induced disordered-ordered transition, where at elevated temperatures both chains exist as random coils with a larger amount of conformational entropy. Upon cooling, entropy is reduced and chains re-orient into a more ordered conformation, which is believed to consist of either a double helix, aggregated mono-helices or aggregated helical dimers (Stone & Nickerson, 2012). κ- and τ-CG also exhibit gelation in the presence of mono- and di-valent cations. In contrast, λ-CG does not gel with either mono- or di-valent cations and displays only viscous behavior. It has been explained that κ- and τ-CG form ordered three-dimensional networks comprising of double helices resulting from "crosslinking" of the adjacent chains in which the sulfate groups are oriented externally. On the other hand, sulfate groups at the 2-postion in λ-CG face inward precluding "crosslinking" and formation of an ordered network (Campo et al., 2009; Running, Falshaw, & Janaswamy, 2012). Nevertheless, a recent research showed that gelation in λ-CG indeed was possible, but with trivalent ions. This novel finding has potential to expand λ-CG's current utility beyond a viscosity enhancing agent (Running et al., 2012). In addition, various types of salts have different effects on the gelling and phase transitions of κ-CG gels and τ-CG gels. It has been reported that stronger κ-CG gels were formed in the presence of KCl compared to other salts such as LiCl, NaCl, $MgCl_2$, $CaCl_2$, and $SrCl_2$ (Kara, Arda, Kavzak, & Pekcan, 2006). Meanwhile, the gel-sol transition temperatures of κ-CG were strongly correlated to NaCl, KCl and $CaCl_2$ contents (Pekcan & Tari, 2008). For τ-CG, storage modulus increased slowly with the monovalent salt concentration and more quickly with the divalent salt concentration. In contrast, for κ-CG, storage modulus increased more rapidly in the presence of KCl than that with calcium or copper. Nevertheless, for high salt concentrations, storage modulus became independent of the type and concentration of cations in the κ-CG solution (Michel, Mestdagh, & Axelos, 1997).

2.3. Biological and toxicological properties of carrageenan

CGs have shown several potential pharmaceutical properties including anticoagulant, anticancer, antihyperlipidemic, and immunomodulatory activities (Campo et al., 2009; Wijesekara, Pangestuti, & Kim, 2011). *In vitro* studies also indicate that CG may also have antiviral effects, inhibiting the replication of hepatitis A viruses (Girond, Crance, Van Cuyck-Gandre, Renaudet, & Deloince, 1991). Additionally, comparison of a variety of compounds reveals that CG is an extremely potent infection inhibitor for a broad range of sexually transmitted human papillomavirus (Buck et al., 2006). There are also indications that CG-based sexual lubricant gels may offer protection against human papillomavirus transmission (Campo et al., 2009; Roberts et al., 2007). CG also exhibits antioxidant activity and free radical scavenging activity. Furthermore, Rocha de Souza et al. found a positive correlation between sulfate content and antioxidant activity (Rocha de Souza et al., 2007).

Since CG is being employed as food additive and pharmaceutical excipient, questions about the safety of CG have been raised. Toxicological properties of CG are as follows: LD_{50} (rat, oral) > 5 g/kg; LD_{50} (rabbit, skin) > 2 g/kg; 4 h LC_{50} (rat, inhalation) > 0.93 mg/L (Weiner, 1991). CG is generally regarded as a relatively nontoxic and nonirritating material when used in nonparenteral pharmaceutical formulations (Rowe et al., 2009). However, CG is known to induce inflammatory responses in laboratory animals for the investigation of anti-inflammatory drugs (Tobacman, 2001; van der Kam, Vry, Schiene, & Tzschentke, 2008), and therefore, its long term safety is a main concern. Studies in recent years showed that long-term administration of CG in various animals caused intestine mucous membrane damage or ulcerous colonitis, and promoted tumor growth (Tobacman, 2001). Thus, it is necessary to perform more epidemiological and essential studies to evaluate the safety of CG (Liang, 2009).

2.4. Carrageenan modification

Although CG has many biological functions, their further utilization in nonfood field is limited by their high viscosity. Therefore, it is desirable to obtain CG oligosaccharides by depolymerization.

CG can be degraded by irradiation with various doses of gamma rays in solid, gel or solution state at ambient temperature. The molecular weights obtained are in the range of 10.5×10^4–0.8×10^4 with narrow distribution. By comparing the yield and susceptibility to degradation, the three types of CGs followed the order of λ > τ > κ in aqueous form (Relleve et al., 2005). However, due to radiation-induced desulfation, CG oligomer has lower sulfate content. In addition, CG can also be degraded by ultrasound or

Table 1
Typical properties of different grades of carrageenans (FMCBioPolymer, 2013b).

Product name	Carrageenan type	Viscosity	Gel type	Water solubility
Gelcarin® GP-379 NF	Iota	High, thixotropic	Elastic, medium strength	Hot
Gelcarin® GP-812 NF	Kappa	Low	Brittle, strong	Hot
Gelcarin® GP-911 NF	Kappa	Low	Brittle, firm	Hot, partial cold
Viscarin® GP-109NF	Lambda	Medium	Non-gelling	Partial cold, full hot
Viscarin® GP-209NF	Lambda	High	Non-gelling	Partial cold, full hot
SeaSpen® PF	Iota	Medium	Elastic, weak	Cold delayed, gel formation

Table 2
Principal characteristics and potential applications of representative carrageenan graft copolymers.

Graft copolymer	Principal characteristics	Potential applications	References
κ-CG-g-N-vinyl-2-pyrrolidone	Better metal ion sorption, better flocculating properties	Super absorbent, flocculant	Mishra, Sand et al. (2010)
κ-CG-g-N-vinyl formamide, and κ-CG-g-vinylsulfonic acid	Resistance to biodegradability, thermally more stable, good swelling towards water	Super absorbent, flocculant	Mishra, Yadav et al. (2010), Yadav et al. (2012)
κ-CG-g-polymethacrylamide	Reversible pH-responsiveness	A novel drug delivery system	Pourjavadi, Sadeghi, and Hosseinzadeh (2004)
Carboxymethyl κ-CG	Better moisture absorption, antibacterial activity	A wound healing material, oral insulin delivery	Fan et al. (2011), Leong et al. (2011)
κ-CG-g-poly(acrylamide)	pH-sensitive	Intestinal targeted drug delivery	Kulkarni, Boppana, Mohan, Mutalik, and Kalyane (2012)

microwave. The existence of a linear relationship between k_n and $[\eta]_n$ suggests that ultrasonic degradation of CGs (κ, τ) follows first-order kinetics during sufficiently short periods. The susceptibility to degradation by low-frequency, high intensity ultrasound (35 kHz, 300 W/cm^2) was in the order of κ-CG > τ-CG (Lii, Chen, Yeh, & Lai, 1999). Similarly, microwave degradation of λ-CG also followed first-order kinetics at lower microwave stress during short periods. The susceptibility to degradation was also related to their molecular size. Furthermore, the stability of glycosidic linkages, concentration, conformation and viscosity of polysaccharides, and microwave stress may have an important influence on the degradation mechanism (Zhou, Yao, & Wang, 2006). In addition, other methods of degradation have also been investigated, such as acid hydrolysis (Myslabodski, Stancioff, & Heckert, 1996), oxidative degradation (Chen et al., 2010), enzymatic hydrolysis using carrageenase (Jouanneau, Boulenguer, Mazoyer, & Helbert, 2010) and commercial enzymes (Wu, 2012). Degradation process can change the biological properties of CG. For example, studies reveal that molecular weight is an important factor that influences the anti-HIV (human immunodeficiency virus) activities of depolymerized CG (Abad et al., 2010; Relleve et al., 2005; Wu, 2012). The oligosaccharides from thickening CG product showed much higher tumor inhibition effect (Hu, Jiang, Aubree, Boulenguer, & Critchley, 2006). Moreover, the oligomers of CG could accelerate wound healing process (Abad et al., 2009). However, on the other hand, it was found that the degraded CG caused significant mucosal ulceration of the colon, leading to increased safety problem (Chen et al., 2010). Therefore, when depolymerized CGs are utilized, their additional biological functions should be considered.

Modification of natural polymers by graft copolymerization is quite promising in order to achieve desirable polymeric properties. Aqueous κ-CG gels display an undesirable large extent of syneresis (the extraction of a liquid from a gel) when subjected to mechanical deformation or aging, a natural process that affects the mechanical and rheological properties of the gel (Campo et al., 2009; Meena, Lehnen, Schmitt, & Saake, 2011). Moreover, κ-CG suffers from drawbacks such as high susceptibility to microbial attack (Mishra, Yadav, Sand, Tripathy, & Behari, 2010). Thus, chemical modifications have been proposed to modulate the physicochemical properties of CG and the grafting mainly occurred at the hydroxyl group of CG (Campo et al., 2009). For instance, covalent binding of other substances to κ-CG chains can produce physically more stable derivatives (Mishra, Sand, Mishra, Yadav, & Behari, 2010). Similarly, specific targeting, swelling and bioactive properties of CG can also be achieved by grafting based on the need for drug delivery. Table 2 summarizes the physicochemical properties and potential applications of representative CG grafted copolymers. In addition to grafting copolymerization, the oversulphated, desulfated, acetylated and phosphorylated derivatives of κ-CG were also reported with various physicochemical properties and biological activities (Xu, Yao, Wu, Wang, & Zhang, 2012; Yuan et al., 2005). More details can be found in a review paper (Campo et al., 2009).

3. Applications of carrageenan in various drug delivery systems

3.1. Oral extended-release tablets

3.1.1. As the single matrix of oral extended-release tablets

Hydrophilic matrix systems are one of the most widely used drug delivery systems to control the release of drugs. Considering the physicochemical properties of CG such as high molecular weight, high viscosity and gelling, CG can be used as the matrix for the preparation of extended-release tablets but with limited drug loading capacity. For instance, a study investigated the potential of two commercial CGs, Gelcarin® GP-379 (τ-CG) and Viscarin® GP-209 (λ-CG) for the preparation of extended-release tablets with tripelennamine HCl as the model drug. Near zero-order release profiles could be obtained by using mixture of equal amount of two carrageenans (τ, λ) with drug loading 10%. However, increasing drug loading to thirty percent resulted in breakup of the tablets during dissolution and departure from zero-order release (Hariharan, Wheatley, & Price, 1997). In addition, κ-CG was also investigated as the matrix of controlled release tablets. Using theophylline monohydrate as the model drug (20%) and microcrystalline cellulose as the filler, influence of κ-CG content on drug release was studied. It was noted that 20% (v/v) κ-CG resulted in fast drug release, slower release was observed at κ-CG content 30% (v/v). Moreover, drug release at 70% (v/v) κ-CG followed zero-order kinetics (Picker, 1999b).

More factors can affect drug release from CG-based matrix tablets. As reported, κ-CG matrix tablets containing 10% theophylline were prepared by direct compression. At 10% CG level, it

appeared that the type of diluents used affected drug release greatly. Tablets with lactose as the diluent released drug faster, compared with that containing dibasic calcium phosphate and microcrystalline cellulose as the diluents. Controlled drug release could be achieved by increasing CG level to 30% and 40%. Meanwhile, dissolution medium could also influence drug release, and the release rate was in the order of pH 7.4 > 0.1N HCl > distilled water (Rosario & Ghaly, 2002). Also, as the rotational speed of the apparatus increases, integrity of the gel layer decreases, leading to increased drug release. Since mono- and di-valent cations can influence the gelation properties of κ- and τ-CG, the added salts (potassium and calcium chloride) to matrices could alter more or less swelling of the matrices and therefore drug release (Picker, 1999a). However, the relationship between drug release and added salts is complicated, depending on the concentrations of cations and the type of drug (Picker, 1999a).

3.1.2. Polymer mixture as the matrix of oral extended-release tablets

When CG is used as the sole matrix material for controlling drug release, sometimes desired release profiles such as zero order release and pH independent drug release, cannot be obtained. Fortunately, polymer mixtures have been widely used for decades in order to modulate drug release in a satisfactory way (Maderuelo, Zarzuelo, & Lanao, 2011). For instance, erosion of λ-CG based matrix tablets can be influenced by pH of the dissolution media. However, by adding more slowly erodible HPMC into λ-CG based matrix, the difference of drug release in dissolution media of varied pH could be reduced (Bonferoni et al., 1994). Furthermore, through optimizing λ-CG/HPMC ratio in the matrix, linear and pH-independent release profile of chlorpheniramine maleate was achieved which lasting for 24 h (Bonferoni et al., 1998). A recent study was also conducted to investigate the effect of polymer blends containing CGs (τ, λ), and cellulose ethers (HPMC, sodium carboxymethyl cellulose, methylcellulose, hydroxypropyl cellulose) on ibuprofen release from tablets prepared by direct compression. Most of the formulations showed linear release profiles ($r^2 \geq 0.96$–0.99) and the release of ibuprofen was sustained over 12–16 h (Nerurkar, Jun, Price, & Park, 2005). In addition, CG in combination with different swollen polymers can also be used to prepare three-layered matrix tablets. Compared with HPMC, pectin, guar gum, xanthan gum, CS, and ethyl cellulose, CG has been regarded as the best polymer for the delivery of metoprolol tartrate in three-layered matrix tablets due to its better accordance to the target release profile, and CG based formulations also exhibited super case II release mechanism (Baloglu & Senyigit, 2010).

On the other hand, since CG is negatively charged above its pK_a value, it can spontaneously associate with positively charged polyions to form polyelectrolyte complexes (Zhang, Mao, & Sun, 2010). Tapia and co-workers employed polyelectrolyte complexes of CS and κ-CG as prolonged drug release matrix. However, the high capacity of κ-CG to absorb water into tablets induced premature disintegration of tablets instead of matrix swelling (Tapia, Corbalan, Costa, Gai, & Yazdani-Pedram, 2005; Tapia et al., 2004). Recent studies showed that, when CS–CGs-based tablets were transferred from simulated gastric fluid to simulated intestinal fluid, *in situ* polyelectrolyte film could be formed on the surface of tablets, and the polyelectrolyte film could further control drug release (Li, Wang, Shao, Ni, et al., 2013; Li, Wang, Shao, Tian et al., 2013). Moreover, the results showed that CS–λ-CG-based matrix was quite promising as controlled-release drug carrier due to its less sensitivity to pH and ionic strength, compared with CS–κ-CG- and CS–ι-CG-based matrix (Li, Wang, Shao, Tian et al., 2013). CG allows a certain degree of ionization maintained even at low pH due to its low pK_a value (Gu et al., 2004b). This property can be used to prepare gastric floating tablets. Bani-Jaber, Al-Aani, Alkhatib, and Al-Khalidi (2011) developed metronidazole loaded floating tablets by using CG and Eudragit® as the matrix and Na bicarbonate as effervescent agent.

3.1.3. As an excipient to extend the release of basic drugs

Due to its half-ester sulfate moieties, CG exhibits a high capacity to react with positively charged substances (Moreno-Villoslada, Oyarzun, Miranda, Hess, & Rivas, 2005). Investigations have shown that CG may interact with some basic drugs, leading to additional decrease in drug release, with burst release suppressed (Kojima, Yoshihara, Sawada, Kondo, & Sako, 2008). An early study showed that λ-CG could control the initial release of salbutamol sulphate, a basic drug, independent of the dissolution media (distilled water, pH 1.2 and 6.8), which was attributed to ionic drug–polymer interaction (Bonferoni et al., 1993). Moreover, the capability of CG in controlling early drug dumping suggests its potential application when constant drug release is desired. A study showed that percent of λ-CG as high as 40% in the matrix (λ-CG–HPMC) provided good early control of drug release (salbutamol sulphate and chlorpheniramine maleate), with release profiles close to linear (Bonferoni et al., 1994). The underlying mechanisms for decreased burst release were elucidated by the fact that when λ-CG-based matrix tablets get contact with dissolution medium, unspecific interaction between basic drug and λ-CG at the tablet surface contributes to reduced drug diffusion, and drug release is mainly governed by erosion of the carriers (Bonferoni, Rossi, Ferrari, & Caramella, 2004; Vadlapatla, Fifer, Kim, & Alexander, 2009). The combination of all mechanisms (water-uptake, erosion and interaction) may result in prolonged drug release of more than 24 h (Pavli, Baumgartner, Kos, & Kogej, 2011; Pavli, Vrecer, & Baumgartner, 2010).

In addition to *in situ* polyelectrolyte complexes formation between basic drug and CG, Bonferoni and Co-workers prepared diltiazem/λ-CG complexes in distilled water, and verified the feasibility of employing λ-CG–diltiazem complexes for controlled drug release (Bonferoni, Rossi, Ferrari, Bettinetti, & Caramella, 2000; Bonferoni, Rossi et al., 2004; Bonferoni et al., 2000; Bonferoni et al., 2008). In both pH 1.2 and 6.8 media, tablets based on physical mixture of diltiazem hydrochloride and λ-CG with drug loading 63% disintegrated quickly and the release was very fast and completed within 1 h. Interestingly, the release of diltiazem from drug/CG complexes based tablets was sustained for more than 20 h (Bonferoni, Rossi et al., 2004). In the tested media, the complexes were able to release the drug completely, suggesting that no dissolution problems would arise with its use in oral dosage forms. Moreover, drug release mechanism from drug/λ-CG complexes based tablets prepared in their work was quite different with that of classical matrix systems, diffusion through hydrated gel layers was reduced. Instead, slow dissolution/erosion of the complexes at tablet surface was likely to be responsible for controlled drug release, while the dissociation of drug–polymer complexes was influenced by the ions in the medium (Bonferoni, Rossi et al., 2004). Further studies showed characteristics of drug/CG complexes were also affected by properties of the drug (Aguzzi et al., 2002). For instance, for the complexes containing more soluble drug such as metoprolol and tramadol, gelation was observed after hydration. In contrast, complexes containing diltiazem apparently did not gel; the behavior of bupropion-containing complexes was in between (Aguzzi et al., 2002).

3.2. As an extrusion aid for the preparation of pellets

Wet extrusion/spheronization are commonly used techniques in pharmaceutical industry for producing pellets (Yoo & Kleinebudde, 2009). Microcrystalline cellulose (MCC) is a standard extrusion aid commonly used to achieve desired properties. However, MCC-based formulations show some disadvantages such

as non-disintegration of the pellets and incompatibility with some drugs (Basit, Newton, & Lacey, 1999). Therefore, it is desirable to find a substitute material for MCC (Jain, Singh, & Amin, 2010).

At present, CG is increasingly used as an extrusion aid (Krueger & Thommes, 2013). Bornhoft and co-workers are the first to evaluate the suitability of different types of CGs as novel extrusion aids (Bornhoft, Thommes, & Kleinebudde, 2005). The κ-type CG, insoluble in cold water, presented suitable plastic and brittle properties for the spheronization process. In contrast, depending on water content, the extrudates based on τ- or λ-CG were either too brittle or too elastic to achieve round pellets in the spheronization process. Anyhow, preliminary trials showed that the addition of calcium, potassium and sodium ions to the granulation liquid could reduce the solubility of τ- and λ-CG and, consequently, allowed successful spheronization process (Bornhoft et al., 2005). By the virtue of these findings, insoluble κ-CG seems to be the most suitable type for extrusion/spheronization. Four process parameters (screw speed, number of die holes, spheronizer speed and spheronizer temperature) have been systematically evaluated for κ-CG-based pellets. The most spherical pellets were obtained with high yield by using a large number of die holes and a high spheronizer speed, and no influence of the investigated process parameters on particle size distribution, mechanical stability, and drug release characteristics was found (Thommes & Kleinebudde, 2007). In addition, for the various types and fractions of fillers investigated (lactose, mannitol, maize starch and dicalciumphosphate dihydrate), only minor effects to the pelletization process and pellet properties were noticed (Thommes & Kleinebudde, 2006a). Meanwhile, using different drugs with high loads (80%) could affect pellet properties as well (Thommes & Kleinebudde, 2007).

Based on the potential of κ-CG as a novel extrusion aid, comparative studies between κ-CG and MCC have been carried out. To produce spherical pellets, higher water content is required for κ-CG compared to MCC. Meanwhile, the range of optimal water content of κ-CG is much broader, which can improve the robustness of the pelletizing process and small fluctuations in powder and liquid feed rate will not affect quality of the product (Bornhoft et al., 2005). Pellets containing up to 90% drug (vatalanib succinate, theophylline) have been successfully prepared by extrusion–spheronization using MCC or κ-CG as matrix former. It was shown that drug release from MCC-based pellets was slow and predominantly controlled by diffusion. In contrast, κ-CG-based pellets disintegrated rapidly upon contact with aqueous media, resulting in rapid release, even in the case of highly dosed drugs with low/poor aqueous solubility (Kranz, Juergens, Pinier, & Siepmann, 2009). Generally, κ-CG-based pellets own lower tensile strength, faster disintegration and drug release compared to MCC-based pellets. Meanwhile, the release profile of κ-CG-based pellets is less affected by the solubility of the drugs (Thommes & Kleinebudde, 2006b). Therefore, κ-CG-based pellets might be able to overcome the bioavailability problem of poorly soluble drugs (Kilor, Sapkal, Awari, & Shewale, 2010). A study showed that the bioavailability of darunavir was substantially improved by using κ-CG-pellets compared with MCC-based pellets (Thommes et al., 2009). On the other hand, due to the high water binding capacity of κ-CG, an expensive drying process may be required and a possible stability problem for sensitive drugs should be noticed (Bornhoft et al., 2005). It was reported that increasing drying temperature and duration decreased the mean dissolution time, tensile strength and disintegration time of the pellets, attributed to a cautious decomposition of κ-CG above 70 °C (Thommes, Blaschek, & Kleinebudde, 2007). In addition, since quick disintegration of κ-CG will lead to fast drug release, a thicker coating and lower amount of pore former are required to achieve sustained release compared with that of MCC-based pellets (Ghanam & Kleinebudde, 2011).

In addition, the compression behavior of κ-CG-based pellets has been investigated. Regardless of their initial components, κ-CG-based pellets exhibited minimal to absent fragmentation and underwent compression by deformation. Compression of pellets with high density silicified MCC as embedding powder could protect the pellets from severe deformation and result in tablets with sufficient tensile strength, minimal friability, negligible elastic recovery and short disintegration time (Ghanam, Hassan, & Kleinebudde, 2010).

3.3. Carrageenan-based micro/nanoparticles delivery systems

3.3.1. Microcapsules

Based on the negative charge, CG is commonly used in combination with cationic charged polymers or cationic polyelectrolyte as the shell of microcapsules. For example, τ-CG was used in combination with spermine to prepare trypsin loaded microcapsules, with functional integrity of trypsin, a hydrolytic enzyme retained at τ-CG concentration below 10.5 mM (Patil & Speaker, 1998). CG was also used together with CS to prepare glucose oxidase loaded microcapsules for oral controlled release (Briones & Sato, 2010). Among the different types of CGs, the order of encapsulation efficiency of CS–CG complexes decreased in the order κ > τ > λ. The CS–κ-CG complex had the lowest release rate and was able to preserve 80.2% of glucose oxidase activity in pH 1.2 solution, 73.3% in chitosanase solution and 66.4% in pepsin solution (Briones & Sato, 2010).

3.3.2. Microspheres

Polymeric microspheres can be employed to deliver drugs in a rate-controlled and sometimes targeted manner. Natural polymers such as CS, alginate, hyaluronic acid, gelatin and starch, are commonly used as the carriers (Mao, Guo, Shi, & Li, 2012a; Mao, Guo, Shi, & Li, 2012b). In contrast, the application of CG in this field is rarely reported. Nevertheless due to the good gelling and film forming properties of some types of CGs, their application in polymeric microspheres field is being explored (Rokka & Rantamaki, 2010). Bonferoni and co-workers prepared timolol maleate loaded λ-CG–gelatin microspheres for ophthalmic delivery. The combination of λ-CG and gelatin in different ratios proved to be useful in modulating the drug release profiles, the rheological properties of the hydrated formulations and their mucoadhesive properties. *In vivo* study in albino rabbits showed that the microsphere formulations had significantly higher drug concentration and bioavailability in the aqueous humour compared with the commercial formulations (Bonferoni, Chetoni et al., 2004). Using CGs (κ, τ) as carriers, mucoadhesive microspheres containing local anesthetic agents and allopurinol have been prepared for the treatment of mucositis, which could form films at air/water interfaces immediately after dropping, implying that the microspheres could uniformly cover inner surfaces of oral cavity to prevent and treat oral mucositis (Tomoda et al., 2009).

3.3.3. Beads

Compared with microcapsules and microspheres, CGs are more extensively reported as the excipients to prepare beads due to their easy gelling, thermo reversibility of the gel network and appropriate viscoelastic properties (Hezaveh, Muhamad, Noshadi, Shu Fen, & Ngadi, 2012). In an early study, κ-CG (Gelcarin® GP-812NF) was used to control the release of acetaminophen from beads prepared by cross-linking technique (Garcia & Ghaly, 1996). Sustained release mefenamic acid-beads based on κ-CG were also employed to reduce daily dose and minimize gastrointestinal disturbance caused by the drug (Ozsoy & Bergisadi, 2000). Sipahigil et al. prepared CGs (κ, τ) beads using ionotropic gelation method as a controlled release system for a slightly water soluble drug

ibuprofen and a freely water soluble drug verapamil hydrochloride. The results showed that about 30% of ibuprofen was released in 6 h, and about 70% of verapamil HCl was released in 5 h from the CG beads prepared (Sipahigil & Dortunc, 2001). The combination of CG with other polymers for the preparation of beads can have additional advantages. For instance, the surface of κ-CG–alginate beads was smoother than that of the one-polysaccharide network beads (Mohamadnia, Zohuriaan-Mehr, Kabiri, Jamshidi, & Mobedi, 2008). Additionally, polyelectrolyte complex hydrogel beads based on CS and CG have been studied as a controlled release device for colon-specific delivery of sodium diclofenac (Piyakulawat, Praphairaksit, Chantarasiri, & Muangsin, 2007).

Moreover, CG-based beads can be used to deliver biological medicine. Enzyme loaded κ-CG beads can be prepared by dropping κ-CG containing enzyme solution into magnetically stirred KCl solution. Shelf-life of alpha-amylase loaded beads was increased up to 3.53 years compared with 0.99 year of the conventional formulation (Sankalia et al., 2006a). Similarly, shelf-life of papain-loaded beads was increased to 3.63 years compared with 1.01 years for the conventional formulation (Sankalia, Mashru, Sankalia, & Sutariya, 2006b). Besides, CG-based hydrogel beads have been used for the controlled delivery of platelet derived growth factor in bone tissue engineering, which satisfied the requirement for a fully functional vascular network (Santo et al., 2009). And, alginate–CG hydrogel beads have been employed as cell delivery systems for regenerative medicine applications (Popa, Gomes, & Reis, 2011).

3.3.4. Nanoparticles

Nanoparticles based on CS–CG complex can be obtained in an aqueous environment under very mild conditions based on electrostatic interaction, avoiding the use of organic solvents or other aggressive processes (Pinheiro et al., 2012). Thus, CS–CG nanoparticles have potential applications not only in drug delivery, but also in tissue engineering and regenerative medicine (Bulmer, Margaritis, & Xenocostas, 2012; Pinheiro et al., 2012). It was reported that CS/κ-CG nanoparticles exhibited noncytotoxic behavior in *in vitro* tests using L929 fibroblasts, and provided a controlled release for up to 3 weeks with ovalbumin as a model protein, and CS/CG ratio had a significant effect on the properties of the nanoparticles (Grenha et al., 2010). Bulmer et al. prepared recombinant human erythropoietin loaded CS–κ-CG nanoparticles through ionotropic gelation process, with encapsulation efficiency of 47.97 ± 4.10% and a sustained *in vitro* release of ~50% over a 2 week period. Studies on the effect of surface charge and CS molecular weight on the encapsulation and controlled release of recombinant human erythropoietin revealed that increasing either parameter could lead to improved encapsulation efficiency and reduced release rate (Bulmer et al., 2012). A recent study showed that CS/κ-CG/tripolyphosphate nanoparticles presented potential for mucosal delivery of macromolecules (Rodrigues, Rosa da Costa, & Grenha, 2012).

3.4. As a stabilizer of micro/nanoparticles

Depending on the concentration and degree of interaction, CG can have either positive or negative effect on protein-stabilized emulsions (Stone & Nickerson, 2012). Stability of whey protein isolate–CG (12:1 mixing ratio) mixed emulsion system, regardless of the CG type (κ, τ, λ), is significantly higher than that of whey protein isolate alone emulsions (Stone & Nickerson, 2012). In another report, emulsions with oil droplets coated by β-lactoglobulin–τ-CG were prepared at pH 6. In the presence of 150 mM NaCl, τ-CG improved the stability of β-lactoglobulin-coated emulsion greatly by preventing surface-denaturation-induced droplet flocculation at temperatures below 60 °C, probably due to the steric stabilization effect provided by τ-CG. However, at higher temperatures the emulsions were highly instable, leading to droplet flocculation, which could be explained by the mechanism that τ-CG desorbed from the droplet surface at high temperature and could not protect them against aggregation induced by thermal denaturation of adsorbed β-lactoglobulin (Gu, Decker, & McClements, 2004a; Gu, Decker, & McClements, 2005). Meanwhile, since CG is anionic polymer with pK_a around 2, pH could influence the properties of β-lactoglobulin stabilized oil-in-water emulsions, and the degree of effect was τ-CG concentration dependent (Gu et al., 2004b). In addition, Rosas-Durazo, Lizardi, Higuera-Ciapara, Argueelles-Monal, and Goycoolea (2011) demonstrated that a nanoemulsion stabilized by dodecyl-trimethylammonium chloride, a commercial cationic surfactant, could be coated with small amount of κ-CG (at molar charge ratio of $Z \leq 0.0045$) by incubation. The successful introduction of κ-CG at the droplet interface offers the possibility to exploit thermoreversible coil-to-helix transition characteristic of κ-CG or other galactan polysaccharides as a strategy to develop temperature-sensitive nanocarriers.

At present, nanosizing techniques have been widely explored to increase the dissolution rate, therefore oral bioavailability of poorly soluble drugs. Using CG as a stabilizer, nanosuspension of a compound/λ-CG complex with a median particle size of about 0.3 μm was successfully developed. The particle size of the nanosuspension did not increase significantly during the lyophilization process and was stable for at least 39 days at room temperature after lyophilization, indicating the potential of CG as a stabilizer in nanosystem (Dai, Dong, & Song, 2007).

3.5. As a gelling agent/viscosity enhancing agent for controlled release and prolonged retention

Based on the physicochemical properties of CG, κ- and τ-CG can form gel easily, especially in the presence of monovalent and divalent ions. Gel formed by τ-CG has suitable rheological and sustained release characteristics, with potential use as vehicles for oral delivery of drugs to dysphagic patients (Miyazaki et al., 2011). Incorporation of magnetic nanoparticles in polysaccharide hydrogels is currently being explored as a strategy to confer novel functionalities to hydrogels valuable for specific bio-applications. κ-CG magnetic hydrogel nanocomposites have been prepared and the effect of magnetic (Fe_3O_4) nanofillers on the release of a model drug (methylene blue) was investigated, demonstrating that the release rate and profile could be tailored with variable Fe_3O_4 nanoparticles load (Daniel-da-Silva et al., 2012). In addition, silver and magnetite nanofillers were synthesized in modified κ-CG hydrogels using *in situ* method. *In vitro* release studies revealed that metallic nanocomposites hydrogels could improve drug release in intestine and limit its release in the stomach (Hezaveh & Muhamad, 2012). On the other hand, CG can be used as a gelling agent when HPMC is used to prepare capsule shell as an alternative of conventional gelatin capsules for oral drug delivery (Jones, Basit, & Tuleu, 2012; Tuleu et al., 2007).

Moreover, many studies focus on adding CG to other polymers in order to utilize the gelling properties of CG to achieve good controlled-release profile. For instance, after κ-CG is added to agarose hydrogels containing micellar drug solution of cetyltrimethylammonium bromide–camptothecin, release rate of the drug decreased significantly (Liu & Li, 2007). Similarly, as 0.02% (w/w) κ-CG is added to agarose gels, with the increase of gel strength and the decrease of drug diffusion rate, the release of model drugs (lidocaine HCl, doxepin HCl, imipramine HCl) remarkably decreased (Caram-Lelham & Sundelof, 1996; Sjöberg, Persson, & Caram-Lelham, 1999).

Considering the gel strength and viscosity of CG, gels based on the combination of CG with other polymers can also be used for different routes of administration, especially in topical drug delivery systems with prolonged retention. *In vivo* drug residence

experiment demonstrated that κ-CG significantly prolonged local residence of acyclovir after vaginal administration in mice and moreover, it showed a synergistic bioadhesive effect with acrylic acid polymer Carbopol® (Liu, Zhu, Wei, & Lu, 2009). Thus, CG-based vaginal drug delivery systems containing topical microbicides were suggested to treat sexually transmitted infections (Li, Zaveri et al., 2013). Similarly, pregelatinized starch gels containing various ratios of κ-CG could offer a wide range of bioadhesive strength, leading to improved physical properties and prolonged buccal delivery of miconazole (Lefnaoui & Moulai-Mostefa, 2011). All-*trans* retinoic acid aqueous gels consisting of ι-CG and polyethylene oxide could be also used for a topical treatment of skin. Polyethylene oxide has a high mucoadhesion property and spinnability, whereas ι-CG has been used as a texture modifier and gelling agent. This reduces the disadvantages of each individual polymer whilst maximizing the optimum properties of each in the resulting combined entity (Kawata, Hanawa, Endo, Suzuki, & Oguchi, 2012). In addition, polymeric system composed of methylcellulose and either κ-CG or τ-CG provided prolonged retention for transscleral delivery of macromolecules (Thrimawithana, Young, Bunt, Green, & Alany, 2011). In a recent report, the permeation-enhancing effect of AT1002, a biologically active fragment of Zonula occludens toxin which could reversibly open intercellular tight junctions after binding to the Zonulin receptor, was significantly promoted by the bioadhesive agent, τ-CG. Administration of ritonavir with AT1002 and CG resulted in a 2.55-fold increase in $AUC_{0\text{-}240min}$ and 2.48-fold increase in C_{max} compared with the control group (Song & Eddington, 2012), The improvement in drug absorption is explained by the fact that τ-CG increased the membrane adhesion of AT1002 and therefore intimate contact with the nasal mucosa (Heinen, Reuss, Saaler-Reinhardt, & Langguth, 2013; Song & Eddington, 2012).

3.6. Others

In addition to the aspects described above, the utilization of CG in the pharmaceutical field is being broadened. For instance, besides as a novel pelletizing agent, CG can also be used as an efficient drug release modifier for ethyl cellulose-coated pharmaceutical dosage forms (Siepmann, Muschert, Leclercq, Carlin, & Siepmann, 2008; Siepmann et al., 2007). Boateng, Pawar, and Tetteh (2013) also demonstrated that polyethylene oxide and κ-CG-based composite film had smooth homogeneous surface, elegant appearance and good transparency. The film dressing containing anti-microbial and anti-inflammatory drugs was effective for wound healing. Interestingly, CG is also employed as an adjuvant to enhance peptide-based vaccine potency (Zhang, Tsai, Monie, Hung, & Wu, 2010).

4. Conclusions and challenges

The application of CG in pharmaceutical field is increasing very fast in the past decade. CG is not only employed for the delivery of small chemical drugs and proteins, but also for tissue regeneration with therapeutic biomacromolecule and cell delivery. At present, it is mainly used 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 CG such as strong negative charge, gelling and viscosity properties, it has been used as a gelling agent/viscosity enhancing agent for controlled drug release and prolonged retention. Other potential applications are being explored. The increasing knowledge of physicochemical properties and structural analysis of CG enables the better utilization of CG as drug carriers. Considering the three most important types of CGs (κ, τ, λ) and distinction in their properties, complexity in drug delivery system design is greatly increased. A suitable type of CG is of great importance for optimal drug delivery. Meanwhile, polymer–drug and polymer–polymer interactions also play a significant role in pharmaceutical formulations development.

Although CG has already been employed as the carrier of drug delivery systems, further analysis of drug delivery mechanisms is still not sufficient. At present, many reports still focus on *in vitro* drug release from CG-based formulations, *in vivo* and *in vitro–in vivo* correlation studies are essential in the near future. Importantly, although CG has been included in USP35-NF30 S1, BP2012 and EP7.0, taking into account its biological properties such as antitumor activities, immunomodulatory effects, anticoagulant activities and inflammatory responses, safety evaluation of CG needs to be richened. Moreover, furthering our current understanding of fundamental properties of CG may provide strong theoretical bases for future application of CG in advanced drug delivery system.

References

Abad, L. V., Kudo, H., Saiki, S., Nagasawa, N., Tamada, M., Fu, H., et al. (2010). Radiolysis studies of aqueous κ-carrageenan. *Nuclear Instruments and Methods in Physics Research Section B*, *268*, 1607–1612.

Abad, L. V., Kudo, H., Saiki, S., Nagasawa, N., Tamada, M., Katsumura, Y., et al. (2009). Radiation degradation studies of carrageenans. *Carbohydrate Polymers*, *78*, 100–106.

Aguzzi, C., Bonferoni, M. C., Fortich, M. R. O., Rossi, S., Ferrari, F., & Caramella, C. (2002). Influence of complex solubility on formulations based on lambda carrageenan and basic drugs. *AAPS PharmSciTech*, *3*, E27.

Baloglu, E., & Senyigit, T. (2010). A design and evaluation of layered matrix tablet formulations of metoprolol tartrate. *AAPS PharmSciTech*, *11*, 563–573.

Bani-Jaber, A., Al-Aani, L., Alkhatib, H., & Al-Khalidi, B. (2011). Prolonged intragastric drug delivery mediated by Eudragit®E-carrageenan polyelectrolyte matrix tablets. *AAPS PharmSciTech*, *12*, 354–361.

Basit, A. W., Newton, J. M., & Lacey, L. F. (1999). Formulation of ranitidine pellets by extrusion-spheronization with little or no microcrystalline cellulose. *Pharmaceutical Development and Technology*, *4*, 499–505.

Bhardwaj, T. R., Kanwar, M., Lal, R., & Gupta, A. (2000). Natural gums and modified natural gums as sustained-release carriers. *Drug Development and Industrial Pharmacy*, *26*, 1025–1038.

Boateng, J. S., Pawar, H. V., & Tetteh, J. (2013). Polyox and carrageenan based composite film dressing containing anti-microbial and anti-inflammatory drugs for effective wound healing. *International Journal of Pharmaceutics*, *441*, 181–191.

Bonferoni, M. C., Chetoni, P., Giunchedi, P., Rossi, S., Ferrari, F., Burgalassi, S., et al. (2004). Carrageenan–gelatin mucoadhesive systems for ion-exchange based ophthalmic delivery: In vitro and preliminary in vivo studies. *European Journal of Pharmaceutics and Biopharmaceutics*, *57*, 465–472.

Bonferoni, M. C., Rossi, S., Ferrari, F., Bertoni, M., Bolhuis, G. K., & Caramella, C. (1998). On the employment of lambda carrageenan in a matrix system. III. Optimization of a lambda carrageenan–HPMC hydrophilic matrix. *Journal of Controlled Release*, *51*, 231–239.

Bonferoni, M. C., Rossi, S., Ferrari, F., Bettinetti, G. P., & Caramella, C. (2000). Characterization of a diltiazem-lambda carrageenan complex. *International Journal of Pharmaceutics*, *200*, 207–216.

Bonferoni, M. C., Rossi, S., Ferrari, F., & Caramella, C. (2004). Development of oral controlled-release tablet formulations based on diltiazem-carrageenan complex. *Pharmaceutical Development and Technology*, *9*, 155–162.

Bonferoni, M. C., Rossi, S., Ferrari, F., Stavik, E., Pena-Romero, A., & Caramella, C. (2000). Factorial analysis of the influence of dissolution medium on drug release from carrageenan-diltiazem complexes. *AAPS PharmSciTech*, *1*, E15.

Bonferoni, M. C., Rossi, S., Tamayo, M., Pedraz, J. L., Dominguez-Gil, A., & Caramella, C. (1993). On the employment of λ-carrageenan in a matrix system. I. Sensitivity to dissolution medium and comparison with Na carboxymethylcellulose and xanthan gum. *Journal of Controlled Release*, *26*, 119–127.

Bonferoni, M. C., Rossi, S., Tamayo, M., Pedraz, J. L., Dominguez-Gil, A., & Caramella, C. (1994). On the employment of λ-carrageenan in a matrix system. II. λ-Carrageenan and hydroxypropylmethylcellulose mixtures. *Journal of Controlled Release*, *30*, 175–182.

Bonferoni, M. C., Sandri, G., Rossi, S., Ferrari, F., Caramella, C., Aguzzi, C., et al. (2008). Polyelectrolyte–drug complexes of lambda carrageenan and basic drugs: Relevance of particle size and moisture content on compaction and drug release behavior. *Drug Development and Industrial Pharmacy*, *34*, 1188–1195.

Bornhoft, M., Thommes, M., & Kleinebudde, P. (2005). Preliminary assessment of carrageenan as excipient for extrusion/spheronisation. *European Journal of Pharmaceutics and Biopharmaceutics*, *59*, 127–131.

Briones, A. V., & Sato, T. (2010). Encapsulation of glucose oxidase (GOD) in polyelectrolyte complexes of chitosan–carrageenan. *Reactive and Functional Polymers*, *70*, 19–27.

Buck, C. B., Thompson, C. D., Roberts, J. N., Mueller, M., Lowy, D. R., & Schiller, J. T. (2006). Carrageenan is a potent inhibitor of papillomavirus infection. *PLoS Pathogens*, *2*, 671–680.

Bulmer, C., Margaritis, A., & Xenocostas, A. (2012). Encapsulation and controlled release of recombinant human erythropoietin from chitosan–carrageenan nanoparticles. *Current Drug Delivery*, *9*, 527–537.

Campo, V. L., Kawano, D. F., Silva, D. B., Jr., & Carvalho, D. I. (2009). Carrageenans: Biological properties, chemical modifications and structural analysis—A review. *Carbohydrate Polymers*, *77*, 167–180.

Caram-Lelham, N., & Sundelof, L. O. (1996). The effect of hydrophobic character of drugs and helix-coil transition of kappa-carrageenan on the polyelectrolyte-drug interaction. *Pharmaceutical Research*, *13*, 920–925.

Chen, H. M., Yan, X. J., Wang, F., Xu, W. F., & Zhang, L. (2010). Assessment of the oxidative cellular toxicity of a κ-carrageenan oxidative degradation product towards Caco-2 cells. *Food Research International*, *43*, 2390–2401.

Coviello, T., Matricardi, P., Marianecci, C., & Alhaique, F. (2007). Polysaccharide hydrogels for modified release formulations. *Journal of Controlled Release*, *119*, 5–24.

Dai, W.-G., Dong, L. C., & Song, Y.-Q. (2007). Nanosizing of a drug/carrageenan complex to increase solubility and dissolution rate. *International Journal of Pharmaceutics*, *342*, 201–207.

Daniel-da-Silva, A. L., Moreira, J., Neto, R., Estrada, A. C., Gil, A. M., & Trindade, T. (2012). Impact of magnetic nanofillers in the swelling and release properties of kappa-carrageenan hydrogel nanocomposites. *Carbohydrate Polymers*, *87*, 328–335.

De Ruiter, G. A., & Rudolph, B. (1997). Carrageenan biotechnology. *Trends in Food Science & Technology*, *8*, 389–395.

Fan, L., Wang, L., Gao, S., Wu, P., Li, M., Xie, W., et al. (2011). Synthesis, characterization and properties of carboxymethyl kappa carrageenan. *Carbohydrate Polymers*, *86*, 1167–1174.

FMCBioPolymer. (2013a). Carrageenan (Introduction). Accessed at http://www.fmcbiopolymer.com/Food/Ingredients/Carrageenan/Introduction.aspx. Date last accessed: 03.10.2013.

FMCBioPolymer. (2013b). Carrageenan (Viscarin, Gelcarin, and SeaSpen). Accessed at http://www.fmcbiopolymer.com/Products/ViscarinGelcarinandSeaSpen/tabid/2954/Default.aspx. Date last. accessed: 03.10.2013.

Garcia, A. M., & Ghaly, E. S. (1996). Preliminary spherical agglomerates of water soluble drug using natural polymer and cross-linking technique. *Journal of Controlled Release*, *40*, 179–186.

Ghanam, D., Hassan, I., & Kleinebudde, P. (2010). Compression behaviour of kappa-carrageenan pellets. *International Journal of Pharmaceutics*, *390*, 117–127.

Ghanam, D., & Kleinebudde, P. (2011). Suitability of kappa-carrageenan pellets for the formulation of multiparticulate tablets with modified release. *International Journal of Pharmaceutics*, *409*, 9–18.

Girond, S., Crance, J. M., Van Cuyck-Gandre, H., Renaudet, J., & Deloince, R. (1991). Antiviral activity of carrageenan on hepatitis A virus replication in cell culture. *Research in Virology*, *142*, 261–270.

Grenha, A., Gomes, M. E., Rodrigues, M., Santo, V. E., Mano, J. F., Neves, N. M., et al. (2010). Development of new chitosan/carrageenan nanoparticles for drug delivery applications. *Journal of Biomedical Materials Research Part A*, *92A*, 1265–1272.

Gu, Y. S., Decker, A. E., & McClements, D. J. (2005). Production and characterization of oil-in-water emulsions containing droplets stabilized by multilayer membranes consisting of beta-lactoglobulin, iota-carrageenan and gelatin. *Langmuir*, *21*, 5752–5760.

Gu, Y. S., Decker, E. A., & McClements, D. J. (2004a). Influence of iota-carrageenan on droplet flocculation of beta-lactoglobulin-stabilized oil-in-water emulsions during thermal processing. *Langmuir*, *20*, 9565–9570.

Gu, Y. S., Decker, E. A., & McClements, D. J. (2004b). Influence of pH and iota-carrageenan concentration on physicochemical properties and stability of beta-lactoglobulin-stabilized oil-in-water emulsions. *Journal of Agricultural and Food Chemisry*, *52*, 3626–3632.

Hariharan, M., Wheatley, T. A., & Price, J. C. (1997). Controlled-release tablet matrices from carrageenans: Compression and dissolution studies. *Pharmaceutical Development and Technology*, *2*, 383–393.

Heinen, C., Reuss, S., Saaler-Reinhardt, S., & Langguth, P. (2013). Mechanistic basis for unexpected bioavailability enhancement of polyelectrolyte complexes incorporating BCS class III drugs and carrageenans. *European Journal of Pharmaceutics and Biopharmaceutics*, *85*, 26–33.

Hezaveh, H., & Muhamad, I. I. (2012). The effect of nanoparticles on gastrointestinal release from modified kappa-carrageenan nanocomposite hydrogels. *Carbohydrate Polymers*, *89*, 138–145.

Hezaveh, H., Muhamad, I. I., Noshadi, I., Shu Fen, L., & Ngadi, N. (2012). Swelling behaviour and controlled drug release from cross-linked kappa-carrageenan/NaCMC hydrogel by diffusion mechanism. *Journal of Microencapsulation*, *29*, 368–379.

Hilliou, L., Larotonda, F. D. S., Abreu, P., Ramos, A. M., Sereno, A. M., & Gonçalves, M. P. (2006). Effect of extraction parameters on the chemical structure and gel properties of κ/ι-hybrid carrageenans obtained from Mastocarpus stellatus. *Biomolecular Engineering*, *23*, 201–208.

Hu, X., Jiang, X., Aubree, E., Boulenguer, P., & Critchley, A. T. (2006). Preparation and in vivo antitumor activity of κ-carrageenan oligosaccharides. *Pharmaceutical Biology*, *44*, 646–650.

Jain, S. P., Singh, P. P., & Amin, P. D. (2010). Alternative extrusion–spheronization aids. *Drug Development and Industrial Pharmacy*, *36*, 1364–1376.

Jiao, G., Yu, G., Zhang, J., & Ewart, H. S. (2011). Chemical structures and bioactivities of sulfated polysaccharides from marine algae. *Marine Drugs*, *9*, 196–223.

Jones, B. E., Basit, A. W., & Tuleu, C. (2012). The disintegration behaviour of capsules in fed subjects: A comparison of hypromellose (carrageenan) capsules and standard gelatin capsules. *International Journal of Pharmaceutics*, *424*, 40–43.

Jouanneau, D., Boulenguer, P., Mazoyer, J., & Helbert, W. (2010). Enzymatic degradation of hybrid ι-/ν-carrageenan by Alteromonas fortis ι-carrageenase. *Carbohydrate Research*, *345*, 934–940.

Kara, S., Arda, E., Kavzak, B., & Pekcan, O. (2006). Phase transitions of kappa-Carrageenan gels in various types of salts. *Journal of Applied Polymer Science*, *102*, 3008–3016.

Kavitha Reddy, G. K. M., Satla, Shobharani, & Gaikwad, Switi. (2011). Natural polysaccharides: Versatile excipients for controlled drug delivery systems. *Asian Journal of Pharmaceutical Sciences*, *6*, 275–286.

Kawata, K., Hanawa, T., Endo, N., Suzuki, M., & Oguchi, T. (2012). Formulation study on retinoic acid gel composed of iota-carrageenan, polyethylene oxide and Emulgen® 408. *Chemical and Pharmaceutical Bulletin*, *60*, 825–830.

Kilor, V. A., Sapkal, N. P., Awari, J. G., & Shewale, B. D. (2010). Development and characterization of enteric-coated immediate-release pellets of aceclofenac by extrusion/spheronization technique using kappa-carrageenan as a pelletizing agent. *AAPS PharmSciTech*, *11*, 336–343.

Knutsen, S. H., Myslabodski, D. E., Larsen, B., & Usov, A. I. (1994). A modified system of nomenclature for red algal galactans. *Botanica Marina*, *37*, 163–169.

Kojima, H., Yoshihara, K., Sawada, T., Kondo, H., & Sako, K. (2008). Extended release of a large amount of highly water-soluble diltiazem hydrochloride by utilizing counter polymer in polyethylene oxides (PEO)/polyethylene glycol (PEG) matrix tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *70*, 556–562.

Kranz, H., Juergens, K., Pinier, M., & Siepmann, J. (2009). Drug release from MCC- and carrageenan-based pellets: Experiment and theory. *European Journal of Pharmaceutics and Biopharmaceutics*, *73*, 302–309.

Krueger, C., & Thommes, M. (2013). Multiple batch manufacturing of theophylline pellets using the wet-extrusion/spheronization process with kappa-carrageenan as pelletisation aid. *Pharmaceutical Development and Technology*, *18*, 225–235.

Kulkarni, R. V., Boppana, R., Mohan, G. K., Mutalik, S., & Kalyane, N. V. (2012). pH-responsive interpenetrating network hydrogel beads of poly(acrylamide)-g-carrageenan and sodium alginate for intestinal targeted drug delivery: Synthesis, in vitro and in vivo evaluation. *Journal of Colloid and Interface Science*, *367*, 509–517.

Lefnaoui, S., & Moulai-Mostefa, N. (2011). Formulation and in vitro evaluation of kappa-carrageenan-pregelatinized starch-based mucoadhesive gels containing miconazole. *Starch-Starke*, *63*, 512–521.

Leong, K. H., Chung, L. Y., Noordin, M. I., Onuki, Y., Morishita, M., & Takayama, K. (2011). Lectin-functionalized carboxymethylated kappa-carrageenan microparticles for oral insulin delivery. *Carbohydrate Polymers*, *86*, 555–565.

Li, L., Wang, L., Shao, Y., Ni, R., Zhang, T., & Mao, S. (2013). Drug release characteristics from chitosan-alginate matrix tablets based on the theory of self-assembled film. *International Journal of Pharmaceutics*, *450*, 197–207.

Li, L., Wang, L., Shao, Y., Tian, Y., Li, C., Li, Y., et al. (2013). Elucidation of release characteristics of highly soluble drug trimetazidine hydrochloride from chitosan-carrageenan matrix tablets. *Journal of Pharmaceutical Sciences*, *102*, 2644–2654.

Li, B., Zaveri, T., Ziegler, G. R., & Hayes, J. E. (2013). User preferences in a carrageenan-based vaginal drug delivery system. *PLoS One*, *8*, e54975.

Liang, A. (2009). Advance on safety evaluation of carrageenan. *China Journal of Chinese Materia Medica*, *34*, 512–514.

Lii, C.-y., Chen, C.-H., Yeh, A.-I., & Lai, V. M. F. (1999). Preliminary study on the degradation kinetics of agarose and carrageenans by ultrasound. *Food Hydrocolloids*, *13*, 477–481.

Liu, J., & Li, L. (2007). Diffusion of camptothecin immobilized with cationic surfactant into agarose hydrogel containing anionic carrageenan. *Journal of Biomedical Materials Research Part A*, *83A*, 1103–1109.

Liu, Y., Zhu, Y.-y., Wei, G., & Lu, W.-Y. (2009). Effect of carrageenan on poloxamer-based in situ gel for vaginal use: Improved in vitro and in vivo sustained-release properties. *European Journal of Pharmaceutical Sciences*, *37*, 306–312.

Maderuelo, C., Zarzuelo, A., & Lanao, J. M. (2011). Critical factors in the release of drugs from sustained release hydrophilic matrices. *Journal of Controlled Release*, *154*, 2–19.

Mao, S., Guo, C., Shi, Y., & Li, L. C. (2012a). Recent advances in polymeric microspheres for parenteral drug delivery—Part 1. *Expert Opinion on Drug Delivery*, *9*, 1161–1176.

Mao, S., Guo, C., Shi, Y., & Li, L. C. (2012b). Recent advances in polymeric microspheres for parenteral drug delivery—Part 2. *Expert Opinion on Drug Delivery*, *9*, 1209–1223.

MarcelTradingCorporation. (2013). What is Carrageenan? Accessed at http://www.marcelcarrageenan.com. Date last accessed: 03.10.2013.

McHugh, D. J. (1987). *Production and utilization of products from commercial seaweeds*. Rome: Food and Agriculture Organization of the United Nations (Chapter 3)

Meena, R., Lehnen, R., Schmitt, U., & Saake, B. (2011). Effect of oat spelt and beech xylan on the gelling properties of kappa-carrageenan hydrogels. *Carbohydrate Polymers*, *85*, 529–540.

Michel, A. S., Mestdagh, M. M., & Axelos, M. A. (1997). Physico-chemical properties of carrageenan gels in presence of various cations. *International Journal of Biological Macromolecules*, *21*, 195–200.

Michel, G., Nyval-Collen, P., Barbeyron, T., Czjzek, M., & Helbert, W. (2006). Bioconversion of red seaweed galactans: A focus on bacterial agarases and carrageenases. *Applied Microbiology and Biotechnology*, *71*, 23–33.

Mishra, M. M., Sand, A., Mishra, D. K., Yadav, M., & Behari, K. (2010). Free radical graft copolymerization of N-vinyl-2-pyrrolidone onto k-carrageenan in aqueous media and applications. *Carbohydrate Polymers*, *82*, 424–431.
Mishra, M. M., Yadav, M., Sand, A., Tripathy, J., & Behari, K. (2010). Water soluble graft copolymer (kappa-carrageenan-g-N-vinyl formamide): Preparation, characterization and application. *Carbohydrate Polymers*, *80*, 235–241.
Miyazaki, S., Ishitani, M., Takahashi, A., Shimoyama, T., Itho, K., & Attwood, D. (2011). Carrageenan gels for oral sustained delivery of acetaminophen to dysphagic patients. *Biological and Pharmaceutical Bulletin*, *34*, 164–166.
Mohamadnia, Z., Zohuriaan-Mehr, M. J., Kabiri, K., Jamshidi, A., & Mobedi, H. (2008). Ionically cross-linked carrageenan-alginate hydrogel beads. *Journal of Biomaterials Science, Polymer Edition*, *19*, 47–59.
Moreno-Villoslada, I., Oyarzun, F., Miranda, V., Hess, S., & Rivas, B. L. (2005). Binding of chlorpheniramine maleate to pharmacologically important alginic acid, carboxymethylcellulose, kappa-carageenan, and iota-carrageenan as studied by diafiltration. *Journal of Applied Polymer Science*, *98*, 598–602.
Myslabodski, D. E., Stancioff, D., & Heckert, R. A. (1996). Effect of acid hydrolysis on the molecular weight of kappa carrageenan by GPC-LS. *Carbohydrate Polymers*, *31*, 83–92.
Nanaki, S., Karavas, E., Kalantzi, L., & Bikiaris, D. (2010). Miscibility study of carrageenan blends and evaluation of their effectiveness as sustained release carriers. *Carbohydrate Polymers*, *79*, 1157–1167.
Necas, J., & Bartosikova, L. (2013). Carrageenan: A review. *Veterinarni Medicina*, *58*, 187–205.
Nerurkar, J., Jun, H. W., Price, J. C., & Park, M. O. (2005). Controlled-release matrix tablets of ibuprofen using cellulose ethers and carrageenans: Effect of formulation factors on dissolution rates. *European Journal of Pharmaceutics and Biopharmaceutics*, *61*, 56–68.
Ozsoy, Y., & Bergisadi, N. (2000). Preparation of mefenamic acid sustained release beads based on kappa-carrageenan. *Bollettino Chimico Farmaceutico*, *139*, 120–123.
Patil, R. T., & Speaker, T. J. (1998). Carrageenan as an anionic polymer for aqueous microencapsulation. *Drug Delivery*, *5*, 179–182.
Pavli, M., Baumgartner, S., Kos, P., & Kogej, K. (2011). Doxazosin–carrageenan interactions: A novel approach for studying drug–polymer interactions and relation to controlled drug release. *International Journal of Pharmaceutics*, *421*, 110–119.
Pavli, M., Vrecer, F., & Baumgartner, S. (2010). Matrix tablets based on carrageenans with dual controlled release of doxazosin mesylate. *International Journal of Pharmaceutics*, *400*, 15–23.
Pekcan, O., & Tari, O. (2008). Cation effect on gel-sol transition of kappa carrageenan. *Polymer Bulletin*, *60*, 569–579.
Picker, K. M. (1999a). Matrix tablets of carrageenans. II. Release behavior and effect of added cations. *Drug Development and Industrial Pharmacy*, *25*, 339–346.
Picker, K. M. (1999b). The use of carrageenan in mixture with microcrystalline cellulose and its functionality for making tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *48*, 27–36.
Pinheiro, A. C., Bourbon, A. I., Medeiros, B. G. D. S., da Silva, L. H. M., da Silva, M. C. H., Carneiro-da-Cunha, M. G., et al. (2012). Interactions between kappa-carrageenan and chitosan in nanolayered coatings—Structural and transport properties. *Carbohydrate Polymers*, *87*, 1081–1090.
Piyakulawat, P., Praphairaksit, N., Chantarasiri, N., & Muangsin, N. (2007). Preparation and evaluation of chitosan/carrageenan beads for controlled release of sodium diclofenac. *AAPS PharmSciTech*, *8*, E1–E11.
Popa, E. G., Gomes, M. E., & Reis, R. L. (2011). Cell delivery systems using alginate–carrageenan hydrogel beads and fibers for regenerative medicine applications. *Biomacromolecules*, *12*, 3952–3961.
Pourjavadi, A., Sadeghi, M., & Hosseinzadeh, H. (2004). Modified carrageenan, 5. Preparation, swelling behavior, salt- and pH-sensitivity of partially hydrolyzed crosslinked carrageenan-graft-polymethacrylamide superabsorbent hydrogel. *Polymers for Advanced Technologies*, *15*, 645–653.
Prado-Fernandez, J., Rodriguez-Vazquez, J. A., Tojo, E., & Andrade, J. M. (2003). Quantitation of kappa-, iota- and lambda-carrageenans by mid-infrared spectroscopy and PLS regression. *Analytica Chimica Acta*, *480*, 23–37.
Relleve, L., Nagasawa, N., Luan, L. Q., Yagi, T., Aranilla, C., Abad, L., et al. (2005). Degradation of carrageenan by radiation. *Polymer Degradation and Stability*, *87*, 403–410.
Rinaudo, M. (2008). Main properties and current applications of some polysaccharides as biomaterials. *Polymer International*, *57*, 397–430.
Roberts, J. N., Buck, C. B., Thompson, C. D., Kines, R., Bernardo, M., Choyke, P. L., et al. (2007). Genital transmission of HPV in a mouse model is potentiated by nonoxynol-9 and inhibited by carrageenan. *Nature Medicine*, *13*, 857–861.
Rocha de Souza, M. C., Marques, C. T., Guerra Dore, C. M., Ferreira da Silva, F. R., Oliveira Rocha, H. A., & Leite, E. L. (2007). Antioxidant activities of sulfated polysaccharides from brown and red seaweeds. *Journal of Applied Phycology*, *19*, 153–160.
Rodrigues, S., Rosa da Costa, A. M., & Grenha, A. (2012). Chitosan/carrageenan nanoparticles: Effect of cross-linking with tripolyphosphate and charge ratios. *Carbohydrate Polymers*, *89*, 282–289.
Rokka, S., & Rantamaki, P. (2010). Protecting probiotic bacteria by microencapsulation: Challenges for industrial applications. *European Food Research and Technology*, *231*, 1–12.
Rosario, N. L., & Ghaly, E. S. (2002). Matrices of water-soluble drug using natural polymer and direct compression method. *Drug Development and Industrial Pharmacy*, *28*, 975–988.
Rosas-Durazo, A., Lizardi, J., Higuera-Ciapara, I., Argueelles-Monal, W., & Goycoolea, F. M. (2011). Development and characterization of nanocapsules comprising dodecyltrimethylammonium chloride and kappa-carrageenan. *Colloids and Surfaces B: Biointerfaces*, *86*, 242–246.
Rowe, R. C., Sheskey, P. J., & Quinn, M. E. (2009). *Handbook of pharmaceutical excipients*. London: Pharmaceutical Press.
Running, C. A., Falshaw, R., & Janaswamy, S. (2012). Trivalent iron induced gelation in lambda-carrageenan. *Carbohydrate Polymers*, *87*, 2735–2739.
Sankalia, M. G., Mashru, R. C., Sankalia, J. A., & Sutariya, V. B. (2006). Stability improvement of alpha-amylase entrapped in kappa-carrageenan beads: Physicochemical characterization and optimization using composite index. *International Journal of Pharmaceutics*, *312*, 1–14.
Sankalia, M. G., Mashru, R. C., Sankalia, J. M., & Sutariya, V. B. (2006). Physicochemical characterization of papain entrapped in ionotropically cross-linked kappa-carrageenan gel reads for stability improvement using Doehlert shell design. *Journal of Pharmaceutical Sciences*, *95*, 1994–2013.
Santo, V. E., Frias, A. M., Carida, M., Cancedda, R., Gomes, M. E., Mano, J. F., et al. (2009). Carrageenan-based hydrogels for the controlled delivery of PDGF-BB in bone tissue engineering applications. *Biomacromolecules*, *10*, 1392–1401.
Siepmann, F., Muschert, S., Leclercq, B., Carlin, B., & Siepmann, J. (2008). How to improve the storage stability of aqueous polymeric film coatings. *Journal of Controlled Release*, *126*, 26–33.
Siepmann, F., Muschert, S., Zach, S., Leclercq, B., Carlin, B., & Siepmann, J. (2007). Carrageenan as an efficient drug release modifier for ethyl cellulose-coated pharmaceutical dosage forms. *Biomacromolecules*, *8*, 3984–3991.
Sipahigil, O., & Dortunc, B. (2001). Preparation and in vitro evaluation of verapamil HCl and ibuprofen containing carrageenan beads. *International Journal of Pharmaceutics*, *228*, 119–128.
Sjöberg, H., Persson, S., & Caram-Lelham, N. (1999). How interactions between drugs and agarose-carrageenan hydrogels influence the simultaneous transport of drugs. *Journal of Controlled Release*, *59*, 391–400.
Song, K.-H., & Eddington, N. D. (2012). The impact of AT1002 on the delivery of ritonavir in the presence of bioadhesive polymer, carrageenan. *Archives of Pharmacal Research*, *35*, 937–943.
Stone, A. K., & Nickerson, M. T. (2012). Formation and functionality of whey protein isolate-(kappa-, iota-, and lambda-type) carrageenan electrostatic complexes. *Food Hydrocolloids*, *27*, 271–277.
Tapia, C., Corbalan, V., Costa, E., Gai, M. N., & Yazdani-Pedram, M. (2005). Study of the release mechanism of diltiazem hydrochloride from matrices based on chitosan–alginate and chitosan–carrageenan mixtures. *Biomacromolecules*, *6*, 2389–2395.
Tapia, C., Escobar, Z., Costa, E., Sapag-Hagar, J., Valenzuela, F., Basualto, C., et al. (2004). Comparative studies on polyelectrolyte complexes and mixtures of chitosan–alginate and chitosan–carrageenan as prolonged diltiazem clorhydrate release systems. *European Journal of Pharmaceutics and Biopharmaceutics*, *57*, 65–75.
Thommes, M., Baert, L., van 't Klooster, G., Geldof, M., Schueller, L., Rosier, J., et al. (2009). Improved bioavailability of darunavir by use of kappa-carrageenan versus microcrystalline cellulose as pelletisation aid. *European Journal of Pharmaceutics and Biopharmaceutics*, *72*, 614–620.
Thommes, M., Blaschek, W., & Kleinebudde, P. (2007). Effect of drying on extruded pellets based on kappa-carrageenan. *European Journal of Pharmaceutical Sciences*, *31*, 112–118.
Thommes, M., & Kleinebudde, P. (2006a). Use of kappa-carrageenan as alternative pelletisation aid to microcrystalline cellulose in extrusion/spheronisation. I. Influence of type and fraction of filler. *European Journal of Pharmaceutics and Biopharmaceutics*, *63*, 59–67.
Thommes, M., & Kleinebudde, P. (2006b). Use of kappa-carrageenan as alternative pelletisation aid to microcrystalline cellulose in extrusion/spheronisation. II. Influence of drug and filler type. *European Journal of Pharmaceutics and Biopharmaceutics*, *63*, 68–75.
Thommes, M., & Kleinebudde, P. (2007). Properties of pellets manufactured by wet extrusion/spheronization process using kappa-carrageenan: Effect of process parameters. *AAPS PharmSciTech*, *8*, E1–E8.
Thrimawithana, T. R., Young, S. A., Bunt, C. R., Green, C. R., & Alany, R. G. (2011). In-vitro and in-vivo evaluation of carrageenan/methylcellulose polymeric systems for transscleral delivery of macromolecules. *European Journal of Pharmaceutical Sciences*, *44*, 399–409.
Tobacman, J. K. (2001). Review of harmful gastrointestinal effects of carrageenan in animal experiments. *Environmental Health Perspectives*, *109*, 983–994.
Tomoda, K., Asahiyama, M., Ohtsuki, E., Nakajima, T., Terada, H., Kanebako, M., et al. (2009). Preparation and properties of carrageenan microspheres containing allopurinol and local anesthetic agents for the treatment of oral mucositis. *Colloids and Surfaces B: Biointerfaces*, *71*, 27–35.
Tuleu, C., Khela, M. K., Evans, D. F., Jones, B. E., Nagata, S., & Basit, A. W. (2007). A scintigraphic investigation of the disintegration behaviour of capsules in fasting subjects: A comparison of hypromellose capsules containing carrageenan as a gelling agent and standard gelatin capsules. *European Journal of Pharmaceutical Sciences*, *30*, 251–255.
Vadlapatla, R., Fifer, E. K., Kim, C.-j., & Alexander, K. S. (2009). Drug–organic electrolyte complexes as controlled release systems. *Drug Development and Industrial Pharmacy*, *35*, 1–11.
van der Kam, E. L., Vry, J. D., Schiene, K., & Tzschentke, T. M. (2008). Differential effects of morphine on the affective and the sensory component of carrageenan-induced nociception in the rat. *Pain*, *136*, 373–379.
Volery, P., Besson, R., & Schaffer-Lequart, C. (2004). Characterization of commercial carrageenans by Fourier transform infrared spectroscopy using single-reflection

attenuated total reflection. *Journal of Agricultural and Food Chemisry*, *52*, 7457–7463.
Weiner, M. L. (1991). Toxicological properties of carrageenan. *Inflammation Research*, *32*, 46–51.
Wijesekara, I., Pangestuti, R., & Kim, S.-K. (2011). Biological activities and potential health benefits of sulfated polysaccharides derived from marine algae. *Carbohydrate Polymers*, *84*, 14–21.
Wu, S.-J. (2012). Degradation of κ-carrageenan by hydrolysis with commercial α-amylase. *Carbohydrate Polymers*, *89*, 394–396.
Xu, L., Yao, Z., Wu, H. G., Wang, F. F., & Zhang, S. X. (2012). The immune regulation of kappa-carrageenan oligosaccharide and its desulfated derivatives on LPS-activated microglial cells. *Neurochemistry International*, *61*, 689–696.
Yadav, M., Sand, A., Mishra, M. M., Tripathy, J., Pandey, V. S., & Behari, K. (2012). Synthesis, characterization and applications of graft copolymer (kappa-carrageenan-g-vinylsulfonic acid). *International Journal of Biological Macromolecules*, *50*, 826–832.
Yoo, A., & Kleinebudde, P. (2009). Spheronization of small extrudates containing kappa-carrageenan. *Journal of Pharmaceutical Sciences*, *98*, 3776–3787.
Yuan, H. M., Zhang, W. W., Li, X. G., Lu, X. X., Li, N., Gao, X. L., et al. (2005). Preparation and in vitro antioxidant activity of kappa-carrageenan oligosaccharides and their oversulfated, acetylated, and phosphorylated derivatives. *Carbohydrate Research*, *340*, 685–692.
Zhang, T., Mao, S., & Sun, W. (2010). Design and in vitro evaluation of a film-controlled dosage form self-converted from monolithic tablet in gastrointestinal environment. *Journal of Pharmaceutical Sciences*, *99*, 4678–4690.
Zhang, Y.-Q., Tsai, Y.-C., Monie, A., Hung, C.-F., & Wu, T. C. (2010). Carrageenan as an adjuvant to enhance peptide-based vaccine potency. *Vaccine*, *28*, 5212–5219.
Zhou, G., Yao, W., & Wang, C. (2006). Kinetics of microwave degradation of λ-carrageenan from Chondrus ocellatus. *Carbohydrate Polymers*, *64*, 73–77.