Carrageenan: a review

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ABSTRACT: Carrageenan is a natural carbohydrate (polysaccharide) obtained from edible red seaweeds. The name Carrageenan is derived from the Chondrus crispus species of seaweed known as Carrageen Moss or Irish Moss in England, and Carraigin in Ireland. Carraigin has been used in Ireland since 400 AD as a gelatin and as a home remedy to cure coughs and colds. It grows along the coasts of North America and Europe. Carrageenans are used in a variety of commercial applications as gelling, thickening, and stabilising agents, especially in food products and sauces. Aside from these functions, carrageenans are used in experimental medicine, pharmaceutical formulations, cosmetics, and industrial applications.

Keywords: carrageenan; pharmacokinetics; toxicity; biological activity

List of abbreviations

3,6-AG = 3,6, anhydro-galactose, **5-HT** = 5-hydroxytryptamine, **6-APA** = 6-amino penicillanic acid, **ADI** = acceptable daily intake, **AG** = amino guanidine, **AIDS** = acquired immune deficiency syndrome, **AT-III** = anti-thrombin-III, **bw** = body weight, **COX-2** = cyclooxygenase-2, **eNOS** = endothelial nitric oxide synthase, **FAO** = food and agriculture organization, **HC-II** = heparin co-factor II, **HIV** = human immunodeficiency virus, **HPV** = human papilloma virus, **HSV** = herpes simplex virus, **IFAC** = international food additives council, **iNOS** = inducible nitric oxide synthase, **JECFA** = Joint FAO/WHO Expert Committee on Food Additives, **L-NMMA** = NG-monomethyl-L-arginine, **nNOS** = neuronal nitric oxide synthase, **NO** = nitric oxide, **NOS** = nitric oxide synthase, **NSAIDs** = non-steroidal anti-inflammatory drugs, **PGs** = prostaglandins, **SSL** = sodium stearoyl lactylate, **TNF-α** = tumour necrosis factor-α

Contents

1. INTRODUCTION

Carrageenan is a generic name for a family of gel-forming and viscosifying polysaccharides, which are obtained by extraction from certain species of red seaweeds (Table 1). Carrageenan is derived from a number of seaweeds of the class Rhodophyceae. This particular type of seaweed is common in the Atlantic Ocean near Britain, Europe and North America. When used in food products, carrageenan has the EU additive E-number E407 or E407a. E407a has a slightly different composition; moreover, it contains a considerable amount of cellulose. Carrageenan has no nutritional value and is used in food preparation for its gelling, thickening, and emulsifying properties (Van de Velde et al. 2002) and in pharmaceutical applications (Takamatsu and Tosa 1993, cited Van de Velde et al. 2002) and experimental medicine this substance is often used for the testing of anti-inflammatory agents (Zacharopoulos and Phillips 1997).

2. Chemical and physical properties of carrageenan

2.1. Chemical structure (Figure 1)

Carrageenan is a sulfated polygalactan with 15 to 40% of ester-sulfate content and an average relative molecular mass well above 100 kDa. It is formed by alternate units of D-galactose and 3,6-anhydro-galactose (3,6-AG) joined by α-1,3 and β-1,4-glycosidic linkage. Carrageenan is classified into various types such as λ, κ, ι, ε, μ, all containing 22 to 35% sulphate groups. This classification was made based on its solubility in potassium chloride. The primary differences which influence the properties of carrageenan type are the number and position of ester sulfate groups as well as the content of 3.6-AG. These names do not reflect definitive chemical structures but only general differences in the composition and degree of sulfation at specific locations in the polymer. Higher levels of ester sulfate mean lower solubil-

Table 1. Characteristics of carrageenan (adopted from: Tobacman 2001)

Chemical composition	hydrocolloid composed of α-D-1,3 and β-D-1,4 galactose residues that are sulfated at up to 40% of the total weight; strong negative charge over normal pH range; associated with ammonium, calcium, magnesium, potassium, or sodium salts
Solubility	λ is readily soluble in cold or hot aqueous solution; κ is soluble in hot solution; treatment of aqueous solution with potassium ion precipitates κ-carrageenan
Gel formation	λ does not form gels; λ and ι form right-handed helices; potassium chloride promotes gel formation of κ; calcium ion promotes gel formation of ι
Metabolism	hydrolysis of glycosidic linkages at lower pH, especially pH ≤ 3.0; also desulfation by sulfatases
Viscosity	near logarithmic increase in viscosity with increasing concentration; viscosity of food-grade carrageenan defined as not less than 5 cps at 75 °C for a 1.5% solution; viscosity ranges from 5 to 800 cps for 1.5% solution at 75 °C
Source	red algae; predominantly aqueous extraction from Chondrus, Gigartina, and various *Eucheuma* species
Molecular weight	discrepancies in definitions; native carrageenan reported to have average molecular weight of 1.5×10^6 to 2×10^7; food-grade carrageenan reported as 100 000–800 000 or 200 000–400 000; degraded carrageenan (poligeenan) has average molecular weight of 20 000–30 000; furcellaran has average molecular weight 20 000–80 000
Properties	λ and κ combine easily with milk proteins to improve solubility and texture; serve as thickening agent, emulsifier, stabilizer
Synergistic effects	with locust bean gum, increase in gel strength; other hydrocolloids may also affect gel strength and cohesiveness
Concentration in food products	0.005–2.0% by weight
Major uses	milk products, processed meats, dietetic formulations, infant formula, toothpaste, cosmetics, skin preparations, pesticides, laxatives

ity temperature and lower gel strength. Kappa type carrageenan has an ester sulfate content of about 25 to 30% and a 3,6-AG content of about 28 to 35%. Iota type carrageenan has an ester sulfate content of about 28 to 30% and a 3,6-AG content of about 25 to 30%. Lambda type carrageenan has an ester sulfate content of about 32 to 39% and no content of 3,6-AG (Barbeyron et al. 2000).

2.2. Properties of carrageenan

The chemical reactivity of carrageenans is primarily due to their half-ester sulfate groups which are strongly anionic, being comparable to inorganic sulfate in this respect. The free acid is unstable, and commercial carrageenans are available as stable sodium potassium and calcium salts or, most
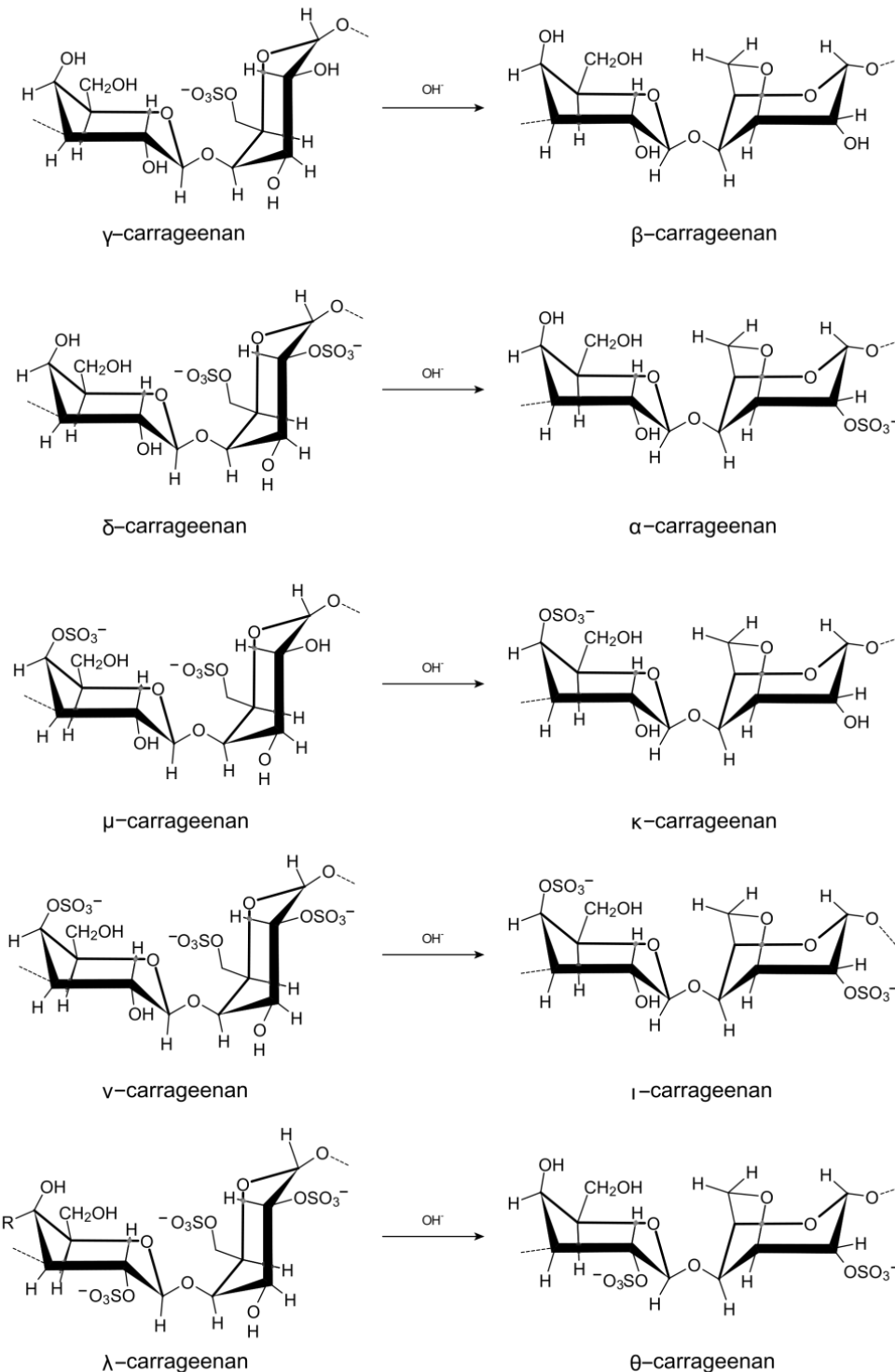

Figure 1. Chemical structure of carrageenans

commonly, as a mixture of these. The associated cations together with the conformation of the sugar units in the polymer chain determine the physical properties of the carrageenans. For example, kappa- and iota-carrageenans form gels in the presence of potassium or calcium ions whereas lambda-carrageenan does not (Michel et al. 1997). The functionality of carrageenans in various applications depends largely on their rheological properties. Carrageenans, as linear, water-soluble, polymers, typically form highly viscous aqueous solutions. Viscosity depends on concentration, temperature, the presence of other solutes, and the type of carrageenan and its molecular weight (Lai et al. 2000). Viscosity increases nearly exponentially with concentration and decreases with temperature. Carrageenans are susceptible to depolymerisation through acid-catalysed hydrolysis. At high temperatures and low pH this may rapidly lead to complete loss of functionality (Stanley 2011).

3. Pharmacokinetics of carrageenan

3.1. Absorption, distribution, metabolism and excretion (ADME)

Many pharmacokinetics studies concerning the oral administration of carrageenans have been conducted in rats (Carey 1958; Hawkins and Yaphe 1965; Dewar and Maddy 1970; Grasso et al. 1973; Tomarelli et al. 1974; Coulston et al. 1975; Pittman et al. 1976; Chen et al. 1981; Nicklin and Miller 1984; Arakawa et al. 1988; Nicklin et al. 1988), guinea-pigs (Grasso et al. 1973; Engster and Abraham 1976), rabbits (Udall et al. 1981) and Rhesus monkeys (Abraham et al. 1972; Mankes and Abraham 1975; Pittman et al. 1976; Abraham et al. 1983). In groups of five rats that received 0.5% native carrageenan *(iota*-carrageenan from *E. spinosum)* or 5% degraded carrageenan for 10 days, faecal excretion and weight gain were similar between the two polymers (Dewar and Maddy 1970), and native carrageenan *(kappa/lambda* from *C. crispus),* untreated or heat-sterilised in milk, was quantitatively excreted in the faeces of rats (Tomarelli et al. 1974). No carrageenan was found in the livers of rats fed 25% native carrageenan *(kappa/lambda* from *C. crispus* or *Iridaea crispata)* in the diet for one month (Chen et al. 1981), of rats fed diets containing 1% or 5% carrageenan *(kappa* from *Gigartina* spp., *iota* from *E. spinosum)* (Coulston et al. 1975), or of rats fed

diets containing 5% *Chondrus crispus* carrageenan *(kappa/lambda)* for 13 weeks (Pittman et al. 1976). No carrageenan was detected in the small or large intestine of rats fed 5% native carrageenan *(iota* from *E. spinosum)* (Grasso et al. 1973). Nicklin and Miller (1984) reported that orally administered carrageenan (type unidentified) of high relative molecular mass could penetrate the mucosal barrier of adult animals via transport by macrophages in Peyer's patches. Carrageenan did not affect the number or distribution of these cells; however, when antigen was administered systematically to carrageenan-fed rats, the antigen-specific antibody response was suppressed. This result suggested that carrageenan interferes with antigen processing by macrophages and thus mollifies normal immune function. Analysis of liver samples from rats fed 25% native carrageenan *(kappa/lambda* from *C. crispus* or *C. iridaea)* in the diet for one month showed that only the second was stored in the liver in two animals, as determined by the presence of *gamma* metachromatic reaction sites in the Kupffer cells (Chen et al. 1981). The results of an additional early study suggested that the *kappa/lambda* form of carrageenan, prepared by a non-standard procedure from either *C. crispus* or *Gigartina stellata,* is not significantly absorbed from the intestine of Wistar rats (Carey 1958). Two additional studies concerning the absorption of carrageenan have been reported (Arakawa et al. 1988; Nicklin et al. 1988); however, in neither report is the identity given of the species from which the carrageenan originated. Moreover, in the latter study the form of carrageenan that was used is unclear (International Food Additives Council 1997). In the first study, rats quantitatively excreted the carrageenan *(kappa* form) in the faeces, and it had the same gel filtration distribution pattern as that of the administered material. In the latter study, in male PVG strain rats given radiolabelled carrageenan *(iota* form), there appeared to have been some uptake into the intestinal wall, Peyer's patches, mesenteric and caecal lymph nodes, and serum; however, the method used to radiolabel the carrageenan with tritium is questionable (International Food Additives Council 1997). Feeding of guinea-pigs with native carrageenan *(iota* from *E. spinosum)* at 5% in the diet for 21–45 days resulted in the accumulation of 36–400 pg/g of caecal or colonic tissue. The carrageenan was contained in macrophages (Grasso et al. 1973). Food-grade carrageenan *(kappa* from *C. crispus, lambda* from

C. rispus, iota from *E. spinosum)* administered to guinea-pigs as a 1% solution in drinking-water for two weeks was not retained in the caecum (Engster and Abraham 1976). It was reported in an abstract that carrageenan (type and species of origin unidentified) was present in the liver, stomach, and small intestine of new-born rabbits given 40 mg native carrageenan orally. Carrageenan was not detected in the cardiac or portal blood 4 h after treatment (Udall et al. 1981). Rhesus monkeys given 1% native carrageenan (*kappa/lambda* from *C. crispus)* in drinking-water for 7–11 weeks, with a subsequent 11-week recovery period, showed no evidence of carrageenan storage (Abraham et al. 1972). In another study on rhesus monkeys, no tissue storage of carrageenan (*kappa/lambda* from *C. crispus)* was found when the monkeys were given 1% native carrageenan in the drinking-water for 10 weeks (Mankes and Abraham 1975). Monkeys receiving daily doses of 500 mg/kg bw native carrageenan (*kappa/lambda* from *C. crispus)* for 15 months excreted 12 µg/ml urine. The concentration was reported to be at the limit of detection of the method (Pittman et al. 1976). Monkeys receiving 50, 200, or 500 mg/kg bw per day native carrageenan (*kappa/lambda* from *C. crispus)* orally for 7.5 years showed no evidence of storage in the liver or other organs (Abraham et al. 1983).

3.2. Degradation of carrageenans in the gastrointestinal tract

Although native carrageenan may be degraded in the gut, this is probably of limited toxicological significance, since, if native carrageenan were sufficiently degraded to cause ulceration or tumour growth, this would have been detected in feeding studies. Since food-grade carrageenan does not have the same effects as degraded carrageenan, it is either not degraded, not degraded to the same molecular mass, or not degraded in the same way. It would appear that carrageenan is only partially degraded, that most of the degradation takes place in the stomach, and that this limited degradation has no effect on the wall of the stomach, where the pH is very low and acid hydrolysis undoubtedly occurs. When a *kappa/lambda* mixture (from an unidentified species) was incubated in simulated gastric juice at pH 1.2 and 37 °C, breakdown of glycosidic linkages was

less than 0.1% after 3 h (Stancioff and Renn 1975). Breakdown of *kappa*-carrageenan (unidentified species) was about 15 times greater than that of the *iota* form; however, the conditions of hydrolysis (6 h at pH 1.0) were more drastic than those that occur normally in the stomach, and the pH would be expected to be considerably higher in a full stomach (Ekstrom and Kuivinen 1983). There is no evidence that carrageenan is degraded in the lower gut. Incubation of a carrageenan solution with the caecal contents of rats for several hours at 37 °C did not alter its viscosity, suggesting that the microbial flora of the rat gut cannot break down carrageenan (Grasso et al. 1973). Degradation of carrageenan by a large number of intestinal bacteria *in vitro* has been reported, but the carrageenan used (of an unidentified form from an unidentified species) contained 20% reducing sugar, which would give a positive result in the test method. Among the bacteria claimed to break down carrageenan were *Klebsiella pneumonia* and *Escherichia coli*; however, both these species can be grown on carrageenan gel (Epifanio et al. 1981). If these bacteria had been able to degrade carrageenan, they would have liquefied the gel medium on which they were grown (Ochuba and von Riesen 1980). Breakdown of food-grade carrageenan (*kappa-*, *lambda-*, and *kappa/lambda*-carrageenan from *C. crispus* and of *iota*-carrageenan from *E. spinosum)* isolated from the faeces of guinea-pigs, rats, and monkeys has been reported, but the site of breakdown was not determined. No intestinal lesions were associated with the breakdown. The molecular mass observed (40–50 kDa) was not as low as that of degraded carrageenan (10–20 kDa) (Pittman et al. 1976). In another study the degradation of food-grade *kappa-* and *iota*-carrageenan was studied under physiologically realistic conditions in an artificial stomach. *Kappa-*carrageenan was not hydrolysed at pH 8 or under the severe conditions of pH 1.2 for 6 h, and the relative molecular mass remained at > 200 kDa, with no more than 20% having a molecular mass of < 100 kDa. It was confirmed that *iota*-carrageenan is more resistant to degradation than the *kappa* form (Capron et al. 1996). The originating species were *E. Cottonii* for *kappa*-carrageenan and *E. spinosum* for *iota*-carrageenan; however, this is not stated in the paper. The greater stability of *iota*-carrageenan to degradation may reflect the conformation of the macromolecule in the medium used (Ekstrom and Kuivinen 1983; Ekstrom 1985; International Food Additives Council 1997). No evidence of fermentation was seen after incubation of rat caecal contents

with *iota*-carrageenan from *E. spinosum* (Grasso et al. 1973). A study in female Wistar rats fed carrageenan (type and origin unidentified) as an inert polysaccharide does not provide quantitative measures of its degradability (Elsenhans et al. 1981). Feeding of three-week-old male Sprague-Dawley rats for four weeks with a diet containing 5% *iota*-carrageenan originating from *E. spinosum* (International Food Additives Council 1997) resulted in a significant reduction in the bacterial population of the caecum, as assessed by bacterial counts and the activity of various caecal microbial enzymes; however, the weights of the caecal contents and the caecal wall were increased (Mallett et al. 1984). Similar effects were seen in mice and hamsters fed dietary *iota*-carrageenan (origin unidentified) (Mallett et al. 1985); however, in neither study was the degradation of carrageenan measured. On the basis of the rates of evolution of methane, hydrogen sulphide, and carbon dioxide from a slurry of mixed human faecal bacteria, carrageenan (origin and type unidentified) was ranked second to fourth in ease of degradation among 15 laxative fibres (Gibson et al. 1990). In a study of 154 bacterial species commonly found in the human colon, carrageenan (origin and type unidentified) was one of the polysaccharides most resistant to fermentation (Salyers et al. 1977).

4. Toxicity of carrageenan

4.1. Acute toxicity

Acute toxicity is summarised in Table 2.

4.2. Short-term studies of toxicity

Groups of two male albino rats fed 0, 5, 10, or 20% *kappa/lambda*-carrageenan from *C. crispus* for 10 weeks grew well, with the exception that 50% of those at the highest dose died (Nilson and Schaller 1941). In groups of male and female rats fed 2, 5, 10, 15, or 20% *kappa/lambda*-carrageenan from *C. crispus* for periods of 23–143 days, the only adverse effect was reduced growth rates at dietary concentrations of 10–20% (Hawkins and Yaphe 1965). No effects on appearance or behaviour were observed in male and female Osborne-Mendel or Sprague-Dawley rats fed 5% *kappa/*

Table 2. Acute toxicity

Carrageenan	Species	Sex	Route	LD_{50} (mg/kg bw)	Reference
kappa/lambda from *C. crispus*	mouse	M/F	oral	9150 ± 440	Food and Drug Research Labs. 1971
NR	rat	NR	intravenous	> 10	Morard et al. 1964
kappa/lambda from *C. crispus*	rat	M/F	oral	5400 ± 260	Food and Drug Research Labs. 1971
kappa/lambda from *C. crispus*	hamster	M/F	oral	6750 ±5 70	Food and Drug Research Labs. 1971
kappa/lambda from *C. crispus*	Guinea-pig	NR	intravenous	> 10	Morard et al. 1964
lambda from *C. crispus* or *G. pistallata*	Guinea-pig	NR	intravenous	< 1	Anderson and Soman 1966
kappa/lambda from *C. crispus*	rabbit	M/F	oral	2640 ± 360	Food and Drug Research Labs. 1971
kappa/lambda from *C. crispus*	rabbit	NR	intravenous	1–20 (LD_{100})	Duncan 1965
NR	rabbit	NR	intravenous	< 50	Morard et al. 1964
Iota*	rat	NR	oral	> 5000	Weiner 1991
Iota*	rat	NR	inhalation	> 930 ± 74 (mg/m^3)	Weiner 1991
Iota*	rabbit	NR	dermal	> 2000	Weiner 1991

NR = not reported; M/F = male and female

*stated to be *kappa/lambda*-carrageenan from *Gigartina radula* (International Food Additives Council 1997)

lambda-carrageenan from *C. crispus* for nine months. Bile-duct proliferation was seen in one male Osborne-Mendel rat, and reduction of the liver lobes and crenation of the margins was observed in three females (Coulston et al. 1976). Groups of 12 male and 25 female Sprague-Dawley rats were fed a diet containing 4% processed, heat-sterilised *kappa/lambda*-carrageenan for six months. There was no effect on growth rate, and the caecum and colon were normal on gross and microscopic examination (Tomarelli et al. 1974). Addition of 5% *iota*-carrageenan from *E. spinosum* to the diet of 10 male Wistar rats for 56 days resulted in slight diarrhoea (Grasso et al. 1973). Groups of 10 adult male albino guinea-pigs were given either water or a 1% solution of undegraded *iota*-carrageenan from *E. spinosum.* After 20 days, two of four treated animals had ulcerative lesions in the caecum, and the remaining six animals had lesions at 30 days. The control group remained healthy (Watt and Marcus 1969). It was reported in a brief letter that 5% *iota*-carrageenan in the diet had the same effect (Sharratt et al. 1970). Administration of 5% *iota*-carrageenan from *E. spinosum* to seven female guinea-pigs in the diet for 56 days resulted in the formation of multiple pin-point caecal and colonic ulcerations (Grasso et al. 1973). Groups of three male and three female Danish Landrace pigs were fed 0, 50, 200, or 500 mg/kg bw per day of *kappa*-carrageenan from *C. crispus* for 83 days. No compound-related deaths were seen, and the behaviour, appearance, and feed intake of the animals remained normal. There were no significant changes in haematological, clinical, chemical, or urinary parameters. Areas of infolding of the intact epithelium with infiltration of the lamina propria of the colonic mucosa by macrophages and lymphocytes were seen in one pig at 200 mg/kg bw per day and two at 500 mg/kg bw per day, but these effects were considered to be reversible (Poulsen 1973). Male and female rhesus monkeys were given drinking-water containing 1% *kappa*-carrageenan from *C. crispus* for 7–11 weeks. The animals remained in good health, and there was no evidence of any adverse effects. One female killed at seven weeks had a grossly normal gastrointestinal tract, but some capillary hyperaemia and mucosal oedema were observed microscopically. A male killed at 11 weeks had no microscopic abnormalities. Two males and two females were allowed an 11-week recovery period and were then given carrageenan at escalating oral doses of 50–1250 mg/kg bw per day

for up to 12 weeks. No gross adverse effects were observed, and the microscopic changes were not attributed to carrageenan (Benitz et al. 1973). Male and female infant baboons were reared from birth to 112 days of age on infant formula containing 0, 1, or 5% *kappa/lambda*-carrageenan derived from *C. crispus.* No effect was seen on organ or body weights, characteristics of the urine and faeces, gross findings, haematological or clinical chemical variables, or the gross or microscopic appearance of the gastrointestinal tract (McGill et al. 1977). Groups of 10 male and 10 female Sprague-Dawley rats were fed 0 or 5% conventionally processed *iota*-carrageenan from *E. spinosum* and *kappa*-carrageenan from *E. cottonii* in the diet for periods of over 90 days. An additional 10 rats of each sex were assigned to a 28-day reversibility phase. The changes observed during the course of the study were attributed by the authors to intake of a diet with a lower nutritional value than the basal diet. The partial reversal of the caecal weight changes during the 28-day reversibility phase and the absence of histopathological changes would support this conclusion (Robbins 1997).

4.3. Long-term studies of toxicity and carcinogenicity

Lifelong administration of *kappa/lambda*-carrageenan from *C. crispus* or *G. mamillosa* at concentrations of 0, 0.1, 5, 15, or 25% in the diet to groups of five male and five female mice of two unidentified strains had no adverse effects (Nilson and Wagner 1959). Lifetime administration of *kappa/lambda*-carrageenan from *C. crispus* or *G. mamillosa* at concentrations of 0, 0.1, 5, 15, or 25% in the diet to groups of five male and five female rats of two unidentified strains resulted in evidence of hepatic cirrhosis, only at the 25% concentration, with no effect on mortality (Nilson and Wagner 1959). Groups of 30 male and 30 female MRC rats were fed 0.5, 2.5, or 5% *kappa*-carrageenan from *C. crispus* in the diet for life; 100 males and 100 females constituted the control group. Animals occasionally developed soft stool consistency, particularly near the start of the experiment. There was a statistically non-significant trend towards an increased incidence of benign mammary tumours and testicular neoplasms in the group fed 2.5% (Rustia et al. 1980). Groups of 15 male and female Sprague-Dawley rats were given extracts

of *kappa*-carrageenan from *Hypnea musciformis* or *Irideae crispata* at a concentration of 1 or 5% in the diet for one year. Weight loss *(P = 0.05)* was observed in all treated rats as compared with the control group, which received alphacel. The livers of rats at 1% were normal on gross and microscopic examination. Gross and microscopic examinations of the livers of rats given 5% *kappa*-carrageenan from *H. musciformis* were normal, except for nodules in two of 12 livers. Gross observation of the livers of rats receiving 5% *kappa*-carrageenan from *I. crispata* showed decreased size, rough surface, and vascularisation in 10/13 rats, which was probably related to treatment. Microscopically, these livers were normal, except for focal necrosis in 1 of 10 livers. There was no evidence of storage of carrageenan-like material (metachromatic) in the liver cells of any of the treated rats, and no fibrillar material was observed by electron microscopy. No changes were observed in the stools of rats receiving 1% of either carrageenan, but female rats given 5% *kappa*-carrageenan from *I. crispata* and males given either carrageenan at the 5% concentration had loose stools. Blood was found sporadically in the stools, but the frequency was not significant (Coulston et al. 1975). Nineteen male and 21 female rhesus monkeys were fed 0, 50, 200, or 500 mg/kg bw *kappa/lambda*-carrageenan by gavage daily on six days a week for five years and carrageenan incorporated into the diet for a further 2.5 years. Loose stools, chronic intestinal disorders, poor appetite, and emaciation were seen in an apparently random distribution. Stool consistency was decreased in a dose-related trend over the entire 7.5 years of the study, and findings of faecal occult blood were increased in a similar fashion. Mean survival time was similar in all groups, and no gross or microscopic changes were detected in the tissues examined. Sporadic differences in body weight from controls were seen randomly; females had significant body-weight depression in the last 2.5 years of the study, which did not appear to be dose-related. No consistent, statistically significant changes occurred in haematological or clinical chemical values, absolute organ weights, or organ-to-body weight ratios after 7.5 years of feeding carrageenan. Cytochemical and ultrastructural observations revealed no storage of carrageenan-like material in livers obtained at biopsy or in other organs obtained at necropsy from monkeys given carrageenan, and no dose-related gross or microscopic changes in other tissues (Abraham et al. 1983).

5. Biological activity of carrageenan

Sulphated polysaccharides from marine algae can have diverse biological and activities including immunomodulatory, anticoagulant, antithrombotic, antiviral and antitumor effects. It has been suggested that these negatively charged molecules, including the sulphated polysaccharides, exert their inhibitory effect by interacting with the positive charges on the virus or on the cell surface and thereby prevent the penetration of the virus into the host cells. It has been reported that carrageenan has no effect on virus attachment or penetration into host cells, but that the synthesis of viral proteins inside the cells was inhibited. Carrageenan has been reported to have anti-HIV activity, but its strong anticoagulant activity is considered to be an adverse reaction when used as a therapeutic drug for AIDS.

5.1. Carrageenan-induced paw oedema

Carrageenan-induced rat paw oedema is a widely used test to determine anti-inflammatory activity and constitutes a simple and routine animal model for evaluation of pain at the site of inflammation without any injury or damage to the inflamed paw (Sugishita et al. 1981; Henriques et al. 1987; Jain et al. 2001; Paschapur et al. 2009; Petersson et al. 2001; Sini et al. 2010). Mouse paw oedema has been increasingly used to test new anti-inflammatory drugs as well as to study the mechanisms involved in inflammation. In the literature, there are about 400 papers reporting the use of mouse paw oedema (Posadas et al. 2004). A freshly prepared solution of 1–3% carrageenan in saline as an intraplantar injection in doses of 50–150 µl is commonly used (Salvemini et al. 1996; Handy and Moore 1998; Nantel et al. 1999; Botting 2000; Rosen et al. 2000; Jain et al. 2001; Guay et al. 2004; Posadas et al. 2004; Naude et al. 2010; Estakhr et al. 2011); higher concentrations have been used for the modelling of specific pathophysiological conditions (Radhakrishnan et al. 2004; Porto et al. 2010; Silva et al. 2010).

The development of oedema in the rat hind paw following the injection of carrageenan has been described as a biphasic, age-weight dependent event in which various mediators operate in sequence to produce the inflammatory response. There are several mediators involved in inflammation. Histamine, serotonine and bradykinin are the first detectable mediators in the early phase of carrageenan-induced

inflammation; prostaglandins (PGs) are involved in the increased vascular permeability and are detectable in the late phase of inflammation. Local and/or systemic inflammation is associated with enhanced levels of the pro-inflammatory cytokines TNF-α, IL-1, and IL-6 (Cuzzocrea et al. 1999). The initial phase of oedema, which is not inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin or aspirin, has been attributed to the release of histamine, 5-hydroxytryptamine (5-HT) and bradykinin. The second accelerating phase of swelling has not only been correlated with the elevated production of prostaglandins, but more recently has been attributed to the induction of inducible cyclooxygenase (COX-2) in the hind paw (Nantel et al. 1999). It can be blocked by the NSAIDs (Handy and Moore 1998). Local neutrophil infiltration and activation also contribute to this inflammatory response by producing, among other mediators, oxygen-derived free radicals such as superoxide anion (O_2^-) and hydroxyl radicals (Salvemini et al. 1996; Posadas et al. 2004).

Another important mediator in acute inflammation is nitric oxide (NO) which is produced in pathological conditions by three distinct isoforms of nitric oxide synthase (NOS): endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS). Carrageenan causes the production and release of NO at the injured site. Perfusion of a non-selective NOS inhibitor, NG monomethyl-ʟ-arginine acetate (L-NMMA), which exhibits some selectivity for inhibition of neuronal and endothelial isoforms, suppressed the release of NO following carrageenan injection in this study. Perfusion of an inducible NOS inhibitor, aminoguanidine hemisulfate (AG), suppressed the release of NO 2.5–8 h after carrageenan injection. Neurectomy completely suppressed NO release for up to 3 h and partially suppressed NO release 4.5–8 h after carrageenan injection. These findings indicate that nNOS contributes to the NO production in both the early and late phase, and that iNOS only contributes to the late phase. The production and release of NO by these NOSs are thought to contribute to tissue injury- and inflammation-induced oedema and hyperalgesia (Handy and Moore 1998; Omote et al. 2001).

5.2. Intestinal inflammation

Watt and Marcus (1971) described a simple method for inducing the formation of ulcers in the large intestine of the guinea pig requiring only the addition of a degraded carrageenan to the drinking water. The method may be used as an experimental model for the study of various aspects of the pathology of ulcerative lesions in this part of the alimentary tract. Freshly prepared, degraded carrageenan was added to the drinking water for guinea pigs to a concentration of 5 %. No greater than 2 g/kg body weight of degraded carrageenan in the drinking fluid for 20 to 45 days results in ulcerative lesions associated with clinical and pathological changes which in certain respects closely resemble ulcerative colitis in man. Clinically there was loss of weight, loose stools, and occult or visible blood in the faeces. Pathologically, ulceration was found in all parts of the large bowel, extensive lesions occurring in the rectum. Microscopically, the similarities include focal mucosal haemorrhages and cellular infiltrates, oedema, crypt abscesses, irregular dilatation of crypts with loss of mucin-secreting cells and degeneration of the lining epithelium, ulceration involving mainly the mucosa, as well as ulcerations in various stages of progression and healing. The ulcerative lesions, however, appear to begin in the caecum and extend distally toward the rectum.

5.3. Anticoagulant and antithrombotic activity

The blood coagulation system consists of intrinsic and extrinsic pathways, with a series of factors involve in the mechanisms. Blood coagulation is promoted by coagulation factors in order to stop the flow of blood though the injured vessel wall in cases of abnormal vascular conditions and exposure to non-endothelial surfaces at sites of vascular injury. As endogenous or exogenous anticoagulants interfere with coagulation factors by inactivating them or restricting their activity, blood coagulation can be prolonged or stopped (Wijesekara et al. 2011). Carrageenan is classified into various types, all containing 22–35% sulphate groups. Many reports exist on the anticoagulant activity of carrageenan. Among the carrageenan types, λ-carrageenan has approximately twice the activity of unfractionated carrageenan and four times the activity of κ-carrageenan. However, the most active carrageenan has approximately one-fifteenth the activity of heparin. The principal basis of the anticoagulant activity of carrageenan appears to be an anti-thrombic property. λ-Carrageenan

showed greater anti-thrombic activity than κ-carrageenan probably due to its higher sulphate content, whereas the activity of the unfractionated material was somewhere between the two. λ-Carrageenan consistently prolonged the clotting time and was more toxic than κ-carrageenan. The difference in sulphate content between the two carrageenans did not correspond directly to differences in anticoagulation action and toxicity (Shanmugam and Mody 2000). As stated above, the mechanism underlying the anticoagulant activity of carrageenan invloves thrombin inhibition. Amidolytic studies initially indicated that the anti-thrombin activity might be mediated via AT-III (anti-thrombin-III), the major mechanism by which heparin acts. In these studies, carrageenans appeared to inhibit amidolysis of thrombin directly and via AT-III; however, only AT-III potentiated X_a amidolysis was observed (Kindness et al. 1979). These interactions may be influenced by certain critical qualities of the polyanionic polymers, i.e., sulphation, size, pattern of ionic substitution and polymer rigidity (Kindness et al. 1979). However subsequent studies using AT-III-depleted plasma showed residual anti-thrombin activity in the presence of carrageenans. λ-Carrageenan has been shown to potentiate the inactivation of thrombin by 'anti-thrombin BM'. These observations would therefore imply that there is either anti-thrombin potentiation via heparin co-factor II (HC-II) and/ or a direct anti-thrombin effect (Kindness et al. 1980a, b; Wunderwald et al. 1979).

5.4. Antiviral activity

Carrageenan is a selective inhibitor of several enveloped viruses, including such human pathogens as human immunodeficiency virus, herpes simplex virus (HSV), human cytomegalovirus, human rhinoviruses and others (Girond et al. 1991; Marchetti et al. 1995; Carlucci et al. 1999; Caceres et al. 2000; Zacharopoulos and Phillips 1997; Stiles et al. 2008). Carrageenan acts primarily by preventing the binding or the entry of virions into cells (Buck et al. 2006, Grassauer et al. 2008). This finding is consistent with the fact that carrageenan resembles heparan sulfate, an HPV cell-attachment factor. Carrageenan extracted from seaweed, is an exceptionally potent inhibitor of papillomavirus infectivity *in vitro*. It was found to be active against a range of common sexually transmitted HPV types

that can cause cervical cancer and genital warts. Carrageenan is also active *in vitro* and in murine model systems against other viruses, including herpes simplex viruses and some strains of HIV-1 (Gonzales et al. 1987; Baba et al. 1988; Lynch et al. 1994; Zeitlin et al. 1997; Witvrouw and De Clercq 1997). However, *in vitro* IC_{50} values for carrageenan inhibition of herpes simplex virus and HIV-1 infectivity are about a thousand-fold higher than the IC_{50s} observed for carrageenan inhibition of genital HPVs *in vitro*.

Carlucci et al. (1997, 2004) reported that the λ-carrageenan and partially cyclised μ-/ι-carrageenan from *Gigartina skottsbergii* showed potent antiviral effect against different strains of herpes simplex virus (HSV) type 1 and type 2. Similar results were reported by Zacharopoulos and Phillips (1997) who described the ability of carrageenan solutions (*lambda, kappa*, or *iota*) to prevent HSV-2 infection and de SF-Tischer et al. (2006).

Leibbrandt et al. (2010) tested a commercially available nasal spray containing *iota*-carrageenan in an influenza A mouse infection model. Treatment of mice infected with a lethal dose of influenza A PR8/34 H_1N_1 virus with *iota*-carrageenan starting up to 48 h post infection resulted in a strong protection of mice similar to mice treated with oseltamivir. Since alternative treatment options for influenza are rare, the nasal spray containing *iota*-carrageenan is an alternative to neuraminidase inhibitors and should be tested for the prevention and treatment of influenza A in clinical trials in humans. Eccles et al. (2010) investigated the efficacy and safety of an *iota*-carrageenan nasal spray in patients with common cold symptoms. Nasal sprays appear to be a promising treatment for safe and effective treatment of early symptoms of the common cold.

5.5. Anti-tumour and immunomodulatory activities

Several studies have reported that carrageenans have antiproliferative activity in cancer cell lines invitro, as well as inhibitory activity of tumor growth in mice (Yuan et al. 2004, 2006; Zhou et al. 2004, 2006; Yuan and Song 2005; Rocha de Souza et al. 2007). In addition, they have antimetastatic activity by blocking the interactions between cancer cells and the basement membrane, inhibit tumor cell proliferation and tumor cell adhesion to various

substrates, but their exact mechanisms of action are not yet completely understood. Yamamoto et al. (1986) reported that the oral administration of several seaweeds can cause a significant decrease in the incidence of carcinogenesis in vivo. Hagiwara et al. (2001) investigated the modifying effects of carrageenan on colonic carcinogenesis in male rats. No treated related changes in clinical signs and body weights were found. Histopathological examination did not demonstrate any enhancement by carrageenan carcinogenesis, carrageenan does not possess any promoting activity at the highest dietary level of 5.0% for colorectal carcinogenesis under the present experimental conditions.

5.6. Other biological activities

The antioxidant activity of all carrageenans has been studied. λ-Carrageenan exhibited the highest antioxidant and free radical scavenging activity. Rocha de Souza et al. (2007) demonstrated a positive correlation between sulfate content and antioxidant activity. The present findings provide a basis for further experiments on the identification and characterisation of specific compounds with relatively high antioxidant activities. Carrageenan from red marine algae is known to be a potent inflammatory agent in rodents and primes mice leucocytes to produce tumour necrosis factor-α (TNF-α) in response to bacterial lipopolysaccharide. Moreover, some types of carrageenans induce potent macrophage activation, while some carrageenans appear to inhibit macrophage functions (Wijesekara et al. 2011). The feeding of Fischer 344 rats on diets containing 15% *kappa/lambda*-carrageenan from *G. radula* resulted in a cholesterol-lowering effect (Reddy et al. 1980). Similar effects of the inclusion of carrageenan in the diet may result in reduced blood cholesterol and lipid levels in human subjects (Panlasigui et al. 2003).

6. Uses of carrageenan

6.1. Industrial uses of carrageenan

Immobilisation of both enzymes and whole cell systems is of major importance in the improvement of the stability, activity and reusability of these biocatalysts. Carrageenan is a suitable support material for the immobilisation of whole cells,

as proven by several applications in different industrial processes. The approval of carrageenan as a food-grade additive and the ease of the immobilisation protocol have promoted its application in the food industries. The mild immobilisation and reaction conditions applied for carrageenan immobilisation of whole cells allows their application in highly (enantio) selective production processes for pharmaceutical compounds and fine chemicals (Van de Velde et al. 2002).

6.2. Industrial food applications

Industrial vinegar production is a biochemical process which utilises bacteria. Osuga et al. (1984) described the use of a bubble-mixed reactor and κ-carrageenan gel beads as carriers for the continuous production of acetic acid. An improvement was attempted through the use of an air-lift reactor (Mori 1993), using the culture of *Acetobacter* species K1024 isolated from a commercial vinegar broth. More recently, a successful continuous production of vinegar was reported using a bubblemixed tabletop bioreactor with κ-carrageenan-immobilised *Acetobacter suboxydans* cells (Tosa and Shibatani 1995). Fermented milk products can be obtained by simultaneous acidification and inoculation of skimmed milk by immobilised mixed cultures. Three different strains of *Lactococcus lactis* and one strain of *Leuconostoc mesenteroides* were separately immobilised in κ-carrageenan/locust bean gum gel (2.75% and 0.25% w/w, respectively) and used in a 2-L stirred reactor (Sodini et al. 1997a, b). Mensour and colleague described the immobilisation system of yeast cells (*Saccharomyces* sp.) for beer production using κ-carrageenan beads continuously produced by a static mixer process (Mensour et al. 1996, 1997). Ethanol production from glucose using cells of *Zymomonas mobilis* immobilised in κ-carrageenan was investigated in a fluidised bed fermenter. This research was extended to study the production of ethanol from starch (Krishnan 1999) using the bacteria co-immobilised with an industrial glucoamylase in carrageenan gel beads and used in a glass column fermenter. The carrageenan gel matrix was reported to provide protection of immobilised *Saccharomyces cerevisiae* cells (Norton et al. 1995) and continuous ethanol production from pineapple cannery waste was attempted using these yeast cells immobilised in κ-carrageenan (Nigam 2000).

6.3. Pharmaceutical applications

6.3.1. Tetracycline and chlorotetracycline production

Tetracyclines represent one of the most important groups of antibiotics and the method normally used for their industrial production is conventional fermentation. Asanza-Teruel et al. (1997) used *Streptomyces aureofaciens* immobilised in κ-carrageenan in an attempt to improve the production of tetracycline and chlorotetracycline.

6.3.2. Semi-synthetic antibiotic production

Semi-synthetic antibiotics are prepared via the coupling of a β-lactam core with the so-called side chain, such as phenylacetic acid, D-phenylglycine, or D-*p*-hydroxyphenylglycine. 6-Aminopenicillanic acid (6-APA) is obtained by the enzymatic hydrolysis of penicillin G produced by fermentation. The suitability of κ-carrageenan as a support for 6-APA production was tested with *E. coli* cells with penicillin-amidase activity (Nagalakshmi and Pai 1997). The cells were immobilised with an efficiency of 90% and could be used for 20 repeated cycles retaining 60% of the initial penicillin-amidase activity. The carrageenan gel beads were hardened with gluteraldehyde. Among the side chains, D-*p*-hydroxyphenylglycine is one of the most important precursors, as it is used for the synthesis of amoxicillin and cefadroxil. Recombinant *E. coli* cells expressing both dihydropyrimidinase and carbamoylase were immobilised in κ-carrageenan and were able to convert D/L-hydroxyphenylhydantoin to D-*p*-hydroxyphenylglycine. In a single-step reaction a conversion of 93% was obtained, while a 20% value was observed with the strain of *Agrobacterium radiobacter*, which contained the original dihydropyrimidinase gene cloned into *E. coli* (Chao et al. 1999).

6.3.3. D-aspartic acid production

A number of D-amino acids have been shown to be important intermediates in drug production. D-Aspartic acid can be used as a component of synthetic penicillins (Takamatsu and Tosa 1993). When D/L-aspartic acid is used as a substrate for the L-aspartate β-decarboxylase of *P. dacunhae* cells, L-aspartic acid is converted to L-alanine but D-aspartic acid remains unchanged due to the high stereospecificity of the biocatalyst. In this way D-aspartic acid and L-alanine can be produced simultaneously using *P. dacunhae* cells immobilised in carrageenan (Takamatsu and Tosa 1993). D/L-Aspartic acid is chemically produced from fumaric acid and ammonia. D-Aspartic acid is crystallised by acidification of the reactor effluent and recovered by centrifugation. L-Alanine is also recovered by centrifugation after crystallisation by the addition of ammonia to the resulting liquor followed by concentration and cooling. This system for the continuous production of D-aspartic acid and L-alanine using *P. dacunhae* cells immobilised in κ-carrageenan has been industrialised since 1988. Industrial application of immobilised whole cells with the use of κ-carrageenan gels for the preparation of L-aspartic acid was first developed by Chibata (Tanabe Seiyaku, Japan) in 1973. The industrial production of a number of other compounds (L-malic acid, L-alanine, L-tryptophan, 1,5-dimethyl-2-piperidone) for use in food and medical applications is based on the same principles (for a detailed discussion see Van de Velde et al. 2002).

6.4. Cleaning of industrial effluents

An efficient integrated nitrogen removal system was developed by the co-immobilisation of *Nitrosomonas europaea* and *Pseudomonas* sp. in κ-carrageenan, taking advantage of the oxygen gradient inside the entrapment beads (Dos Santos et al. 1996a, b). The immobilisation of *M. aurum* in κ-carrageenan and its use in an air-bubble fermenter resulted in an improvement of its morpholine-degrading capacity (Swain et al. 1991; Poupin et al. 1996). The carrageenan gel and immobilised microbial cells method was used for 4-chlorophenol degradation (Wang et al. 1997). Aerobic and anaerobic microbial communities have also been co-immobilised into κ-carrageenan/gelatin gel beads (Gardin and Pauss 2001). Under air-limited conditions these immobilisates catalyse the degradation of 2,4,6-trichlorophenol. Pentachlorophenol pesticide degradation in contaminated soil was attempted with the use of *Pseudomonas* sp. UG30 cells immobilised in κ-carrageenan (Cassidy et al. 1997).

6.5. Other uses of carrageenan

In the language of food chemists, carrageenan is variably called an emulsifier, stabiliser, colloid, or gum. Many products that we now take for granted – especially soymilk, chocolate and other flavoured milks, dairy products, infant formulas, and nutritional supplement beverages rely upon carrageenan for their uniform consistencies. They could not be made, packaged and stored for long periods of time without this ingredient.

Carrageenans are used to gel, thicken, or suspend; therefore they are used in emulsion stabilisation, for syneresis control, and for bodying, binding and dispersion. The major uses are in foods, particularly dairy applications. Furcellaran generally finds applications similar to those for *kappa*-carrageenan. Historically, furcellaran has dominated two major European application fields: tart or cake glaze powders and flan powders. Today the special properties of excellent gel texture and flavour release make furcellaran a preferred product for use in milk pudding powders. Carrageenan is unique in its ability to suspend cocoa in chocolate milk at very low concentrations (ca. 300 ppm); no other gum has been found to match it. A very delicate milk gel structure, undetectable on pouring or drinking the milk, is believed to hold the cocoa in suspension. A substantial differential between the concentrations at which settling of cocoa occurs and that at which visible gelation is evident is required for practical stabilisation. This is achieved by careful selection of weed type and quality. *Iota*-carrageenans which have textures very similar to those of gelatin gels are used in dessert gel formulations. They have an advantage over gelatin gels in that their melting point is higher, making them more suitable in tropical climates or where refrigeration is not available. This is offset to some extent by the different texture, since these gels do not "melt in the mouth", as does gelatin. However, a further advantage is that *iota* gels retain their tender structure on aging, whereas gelatin tends to toughen. This is important for ready-to-eat desserts, popular in Europe. *Kappa*-carrageenan or furcellaran by itself is unsatisfactory for dessert gel applications due to the "short", brittle structure of its gel. This can be ameliorated by the incorporation of locust bean galactomannan into the formulation, and *kappa*-locust bean or *iota- kappa*-locust bean blends are also offered for this application. To achieve sparkling-clear gels it is necessary to use a locust bean gum which has

been clarified by filtration. The clarified gum is produced for this purpose by several of the major carrageenan manufacturers.

In toothpastes carrageenans function as a "binder" to impart the desired rheological properties to the paste and to provide the cosmetic quality of "sheen". Toothpastes consist of ingredients which interact in complex and in poorly understood ways and the carrageenan often must be carefully tailored to achieve satisfactory performance in a particular formulation. Carrageenan suffers severe competition in the U.S. domestic market from sodium carboxymethylcellulose, a much cheaper gum. Despite this, business has been retained – and regained – due to the superior quality and appearance carrageenan imparts to toothpastes. Outside the United States carrageenan has maintained a strong position in this application, due, among other factors, to its immunity to degradation by enzymes which attack cellulose gums. Gelatinous extracts of the *Chondrus crispus* (Irish Moss) seaweed have been used as food additives for hundreds of years. Carrageenan is a vegetarian and vegan alternative to gelatin.

When used in food products, carrageenan has the EU additive E-number E407 or E407a when present as "processed eucheuma seaweed", and is commonly used as an emulsifier. In parts of Scotland (where it is known as (An) Cairgean in Scottish Gaelic) and Ireland (variety used is Chondrus Crispus known in Irish Gaelic variously as carraigín [little rock], fiadhain [wild stuff], cluimhin cait [cat's puff], mathair an duilisg [mother of seaweeds], ceann donn [red head]), it is known as Carrageen Moss. It is boiled in milk and strained, before sugar and other flavourings such as vanilla, cinnamon, brandy, or whisky are added. The end-product is a kind of jelly similar to pannacotta, tapioca, or blancmange. When *iota*-carrageenan is combined with sodium stearoyl lactylate (SSL), a synergistic effect is created, allowing for stabilising/emulsifying not obtained with any other type of carrageenan (*kappa/lambda*) or with other emulsifiers (mono and diglycerides, etc.). SSL combined with *iota* carrageenan is capable of producing emulsions under both hot and cold conditions using either vegetable or animal fat.

The use of carrageenan in the food industry is often discussed in the context of its safety. Authorities worldwide such as JECFA, Scientific Community on Food (SCF), and International Food Additives Council (IFAC) have extensively evaluated the

safety of carrageenan. In contrast to the findings presented by Tobacman (2001) and Tobacman et al. (2001) all of these authorities agree that carrageenan is safe for use in foods. In 1978, the Scientific Committee for Food (SCF) endorsed the Acceptable Daily Intake (ADI) of 0–75 mg/kg bw established for carrageenan by the Joint FAO/WHO Expert Committee on Food Additives (JECFA 1974; SCF 1978).

7. CONCLUSION

Carrageenans are commercially important hydrophilic colloids (water-soluble gums) which occur as matrix material in numerous species of red seaweeds (Rhodophyta) wherein they serve a structural function analogous to that of cellulose in land plants. Chemically they are highly sulfated galactans. Due to their half-ester sulfate moieties they are strongly anionic polymers. The chemical reactivity of carrageenans is primarily due to their half-ester sulfate groups which are strongly anionic, being comparable to inorganic sulfate in this respect. The free acid is unstable, and commercial carrageenans are available as stable sodium potassium and calcium salts or, most commonly, as a mixture of these. The associated cations together with the conformation of the sugar units in the polymer chain determine the physical properties of the carrageenans. The functionality of carrageenans in various applications depends largely on their rheological properties. Viscosity depends on concentration, temperature, the presence of other solutes, and the type of carrageenan and its molecular weight. Viscosity increases nearly exponentially with concentration. Most of the toxicological studies in which an identifiable type of carrageenan and an identifiable seaweed species were used were undertaken with *kappa*- or *kappa/lambda*-carrageenan from *C. crispus.* The results of the few parallel studies suggest that there are no large differences in the effects of the different forms of carrageenan or in the effects of carrageenans prepared from different species of seaweed. Carrageenans have very low toxicity, and have been shown not to be teratogenic. Carrageenan is used in many dairy products such as cream cheese, cottage cheese, skimmed milk, and yogurt as well as desserts and sweets such as custards, ice cream, milk shakes, pie fillings and chocolate products. In addition to use as a food additive, carrageenan is also used in air freshener gels, toothpaste, fire fighting foam, shampoo, cosmetic creams and shoe polish. In biotechnology, carrageenan is used as a gel to immobilise cells/enzymes. A special use of carrageenan is in experimental medicine for the testing of anti-inflammatory drugs.

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