Carbohydrate Polymers 79 (2010) 1157–1167

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Miscibility study of carrageenan blends and evaluation of their effectiveness as sustained release carriers

Stavroula Nanaki [a], Evangelos Karavas [b], Lida Kalantzi [b], Dimitrios Bikiaris [a,*]

[a] Laboratory of Organic Chemical Technology, Department of Chemistry, Aristotle University of Thessaloniki, GR-541 24 Thessaloniki, Greece
[b] Pharmathen S.A., Pharmaceutical Industry, Dervenakion Str. 6, Pallini Attikis, GR-153 51 Attiki, Greece

ARTICLE INFO

Article history:
Received 25 August 2009
Received in revised form 22 October 2009
Accepted 26 October 2009
Available online 31 October 2009

Keywords:
Carrageenans
Polymer blends
Solid dispersions
Tolterodine L-Tartrate
Controlled release

ABSTRACT

Polymeric matrices of ι-, κ- and λ-carrageenans and ι-, κ- and λ-carrageenans blends, prepared by simple mixing and by solvent evaporation technique, have been tested for controlled release delivery of Tolterodine L-Tartrate. X-ray diffraction (XRD), infrared spectroscopy (FT-IR), scanning electron microscopy (SEM) and viscometry measurements showed that although all weight ratios of carrageenans blends were immiscible, carrageenans formed complexes with the drug through hydrogen bonding. In solid dispersions formulations although the drug was almost immediately dissolved (due to its amorphous character), an amount remained absorbed into polymer matrix and was not released, probably due to hydrogen bonding. When physical mixtures of pure carrageenans and Tolterodine L-Tartrate were prepared, release rate was slower and when λ-carrageenan was used, an almost controlled release formulation was achieved. However, real controlled release formulations were achieved only when physical mixtures of ι-/λ-carrageenans and Tolterodine were used. Thus, the combination of different types of carrageenans could change the carrier's behaviour.

© 2009 Elsevier Ltd. All rights reserved.

1. Introduction

Hydrophilic polymers hydrate, swell and/or dissolve in aqueous environment and for that reason they have been extensively used as excipients in drug formulations (Gupta, Hariharan, Wheatley, & Price, 2001). Carrageenan for example, is a hydrophilic polymer with various applications in pharmaceutical formulations. The name carrageenan however, does not refer to a single biopolymer but to a family of water-soluble sulfated polysaccharides (linear macromolecules). More specifically, carrageenans are sulfated galactans extracted from red seaweed (*Rhodophycae*), mostly of the genus *Chondrus*, *Eucheuma*, *Gigartina* and *Iridaea*. Different seaweeds produce different carrageenans. They are composed of D-galactose residues linked alternately in 3-linked-β-D-galactopyranose and 4-linked-α-D-galactopyranose units and they are classified according to the degree of the 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. The three most important carrageenans (important from commercially point of view) differ on the degree of sulfation (15–40%) and they are traditionally identified by a Greek prefix: ι- (iota) carrageenan (mono-sulfate), κ- (kappa) carrageenan (di-sulfate), and λ- (lambda) carrageenan (three-sulfate) (Fig. 1) (van de Velde & De Ruiter, 2005, chap. 10).

ι-Carrageenan is approximately 32% substituted with ester sulfate groups and is soluble in hot water, forming solutions exhibiting thixotropic characteristics. κ-Carrageenan is approximately 25% substituted by ester sulfate groups and is soluble in hot water. λ-Carrageenan is approximately 35% substituted by ester sulfate groups, is partially soluble in cold water and fully soluble in hot water. As can be seen from their chemical structures, 3,6-anhydro bridges are present in ι- and κ-carrageenans but not in λ-carrageenan. The presence or absence of the anhydro bridges leads to different rheological behaviours; ι- and κ-carrageenan have the ability to form gels, whereas λ-carrageenan acts as a thickener/viscosity agent. Carrageenans' viscoelastic behaviour and physical properties, either alone or when in mixtures with other substances, have been extensively studied (Bonferoni et al., 1993; Picker, 1999a, 1999b, 1999c; Picker & Gabelick, 1997).

In addition to the rheological behaviour, the coil–helix transition temperature is a physical property of carrageenans that needs to be studied. Both ι- and κ-carrageenans have two forms: (i) the unstructured random coil that typically occurs at elevated temperatures and (ii) the structured double helix that is usually formed under cooling. Random coils form double helices at a specific temperature during the cooling of a hot carrageenan solution. This temperature is called coil–helix transition temperature and it is an important parameter of the functional properties of carrageen-

* Corresponding author. Tel.: +30 2310 997812; fax: +30 2310 997667.
E-mail address: dbic@chem.auth.gr (D. Bikiaris).

0144-8617/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carbpol.2009.10.067

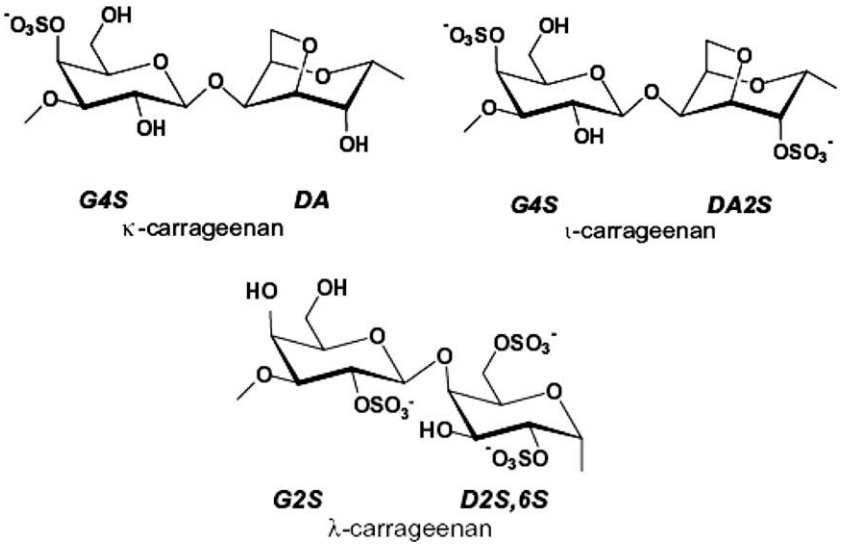

Fig. 1. Schematic representation of idealized repeating units of carrageenans.

ans. ι- and κ-carrageenans have coil–helix transition temperature at 45 °C and at 38 °C, respectively, in water, while λ-carrageenan (a) does not form helices, (b) is always present in the random coil conformation and (c) cannot form gels (van de Velde & De Ruiter, 2005).

Complexes between carrageenan and drug molecules have been proved to control the drug's release rate and, thus, carrageenans, as well as carrageenan mixtures, have been used as drug carriers (Bonferoni, Rossi, Ferrari, Bettinetti, & Caramella, 2000; Bonferoni et al., 1993, 1994; Bonferoni et al., 1998; Bonferoni, Rossi, Ferrari, Stavik et al., 2000; Hariharan, Wheatley, & Price, 1997; Nakano & Ogata, 1984; Picker, 1999a, 1999b, 1999c; Picker & Gabelick, 1997). Various studies have been published on kappa and iota carrageenan blends (Ridout, Garza, Brownsey, & Morris, 1996; Villanueva, Mendoza, Rodrigueza, Romero, & Montano, 2004), on mixtures of carrageenan with xanthan gum (Rodriguez-Hernandez & Tecante, 1999), and on mixtures of carrageenan with gelatin (Michon, Cuvelier, Launay, & Parker, 1996). Complexes of carrageenan with chitosan (Shumilina & Shchipunov, 2002; Tapia, Corbalan, Costa, Gai, & Yazdani-Pedram, 2005; Tapia et al., 2004) and of λ-carrageenan with hydroxypropylmethylcellulose (Bonferoni et al., 1993, 1994, 1998) have also been used for controlling the drug's release profile. Finally, complexes between different types of the same carrageenan have been used for the same reason (Hernandez, Dolz, Dolz, Delegido, & Pellicer, 2001).

The aim of the present study was to prepare polymer blends of ι-, κ- and λ-carrageenans and investigate the possibility of them being better carriers for sustained release formulations of Tolterodine L-Tartrate compared to the pure carrageenans. Tolterodine L-Tartrate was selected as a model drug. Tolterodine (Fig. 2) is used for the treatment of overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence. Tolterodine L-Tartrate is slightly soluble in water, soluble in methanol, slightly soluble in ethanol and practically insoluble in toluene, has a melting point of 206–212 °C and a dissociation constant (pK_a) of 9.9 (Moffat et al., 2004). In clinical practice, sustained release formulations of Tolterodine are preferred over the immediate release formulations.

Formulations of Tolterodine with carrageenans were prepared either as physical mixtures or using a solid dispersion technique. Miscibility and several other physicochemical characteristics of the prepared blends were studied.

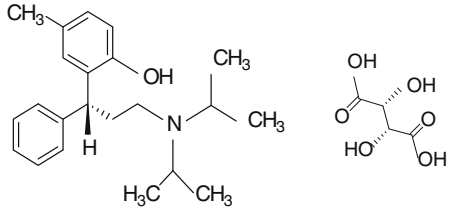

Fig. 2. Chemical structure of Tolterodine L-Tartrate.

2. Experimental

2.1. Materials

Carrageenans like Gelcarin GP-379NF (ι-carrageenan), Gelcarin GP-812NF (κ-carrageenan) and Viscarin GP-209NF (λ-carrageenan) are naturally-occurring families of carbohydrates extracted from red seaweed and were kindly supplied by FMCBioPolymer (Netherlands). Tolterodine L-Tartrate [(+)-(R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenyl-propylamine L-Tartrate] is a white crystalline powder with a molecular weight of 475.6 g/mol, melting point 210 °C, slightly soluble in water (12 mg/L at 25 °C) but soluble in methanol. Tolterodine L-Tartrate was 99.7% pure and it was supplied by Ferrer S.A. (Barcelona, Spain). All other materials and solvents used for the analytical methods were of analytical grade.

2.1.1. Preparation of carrageenans' blends

Carrageenans' polymer blends were prepared using the solvent evaporation technique. Each carrageenan (ι-, κ- and λ-) was initially dissolved in distilled water by stirring at 80 °C forming solutions of 0.5% w/v. Proper amounts of each solution were mixed, preparing solutions κ/λ, κ/ι and ι/λ having ratios 0/100, 20/80, 40/60, 60/40, 80/20 and 100/0 w/w, i.e. six different mixtures for every blend were prepared. Excessive water was removed at 60 °C temperature under vacuum. After drying, the blends formed cast films.

2.1.2. Preparation of carrageenans' physical mixtures

Proper amounts of carrageenans ι- and λ- were mixed together forming concentrations 20/80, 40/60 and 80/20 w/w. The total amount of each mixture was 200 g.

2.2. Polymer blends characterization

2.2.1. X-ray diffraction (XRD)

XRD analysis was performed on cast films, which were scanned over the interval of 5–55° 2θ, using a Phillips PW1710 diffractometer with Bragg–Brentano geometry (θ, 2θ) and a Ni-filtered CuKa radiation.

2.2.2. Fourier transformation-Infrared spectroscopy (FT-IR)

Five milligrams of scrapped film were mixed with 180 mg of KBr in an agate mortal. The mixture was pressed under 5 tons for 2 min and a pellet was formed. The pellet was then placed into an attachment in the optical compartment and FT-IR spectra were obtained using a Perkin-Elmer FT-IR spectrometer (Spectrum 1). Infrared (IR) absorbance spectra were obtained between 500 and 4000 cm^{-1} at a resolution of 4 cm^{-1} using 20 co-added scans. All spectra presented are baseline corrected and normalized.

2.2.3. Differential scanning calorimetry (DSC)

A Perkin-Elmer, Pyris 1 differential scanning calorimeter (DSC), calibrated with Indium and Zinc standards, was employed. A sample of about 10 mg was used for each test, placed in scaled aluminum pan and heated to 80 °C at a heating rate of 20 °C/min. The sample was held at that temperature for 5 min in order to erase any thermal history. After that it was quenched to −60 °C with liquid nitrogen and scanned immediately to 80 °C at a heating rate of 5 °C/min.

2.2.4. Scanning electron microscopy (SEM)

The morphology of the prepared blends was examined using a scanning electron microscope (SEM), type Jeol (JMS-840). For this examination the fractured samples of polymer blends prepared under liquid nitrogen were used. All the studied surfaces were coated with carbon black to avoid charging under the electron beam.

2.2.5. Viscosity measurements

Intrinsic viscosity [η] of carrageenans and carrageenan blends was measured using an Ubbelohde viscometer at 30 °C in distilled water solutions.

2.3. Drug loading of carrageenans, their blends and their physical mixtures

Tolterodine L-Tartrate was dissolved in methanol while neat ι-, κ- and λ-carrageenans were dissolved in distilled water. The two solutions (Tolterodine solution and one carrageenan solution each time) were mixed under gently stirring at room temperature. The solvent was removed by heating the solutions at 50 °C for 24 h under vacuum. Solid dispersions containing 2.5, 5.0, 7.5 and 10 wt.% of Tolterodine formed thin films, which were then milled to particles having sizes of 100–250 μm. These particles were used for the drug release studies. The same procedure was followed to prepare solid dispersion of Tolterodine and the carrageenan blends (κ/λ, κ/ι and ι/λ).

Physical mixtures of Tolterodine L-Tartrate with each carrageenan (ι-, κ- and λ-) and with ι/λ mixtures referred above (Section 2.1.2) were also prepared. The proper amount of Tolterodine L-Tartrate was added to pure carrageenans and their ι/λ mixtures at concentrations 2.5, 5.0, 7.5 and 10.0 wt.%.

2.4. Characterization of carrageenans drug formulations

2.4.1. Physical state characterization

The physical state of the formulations containing carrageenans and Tolterodine L-Tartrate was described using XRD, FT-IR spectroscopy and SEM, as described before.

2.4.2. Preparation of pellets

Hundred milligrams of each formulation were inserted into an adequate matrix and compressed for 2 min under 5 tons. Pellets were formed and used for the in vitro release studies.

2.4.3. In vitro release profile

In vitro release rates of Tolterodine from the prepared formulations were generated in USP dissolution apparatus II (paddle apparatus). Dissolution tests were performed in phosphate buffer, pH 6.8, at 37 ± 1 °C, the rotation speed was set at 100 rpm, and the dissolution medium was 1000 mL. All dissolution studies were performed in triplicate. The dissolution apparatus used, was a DISKTEK 2100C with an auto sampler DISTEK EVOLUTION 4300 and a DISKTEK syringe pump.

2.4.4. HPLC quantitative analysis

Quantitative analysis was performed using a Shimadzu HPLC prominence system consisted by a degasser (DGU-20A_5), a liquid chromatograph (LC-20 AD), an auto sampler (SIL-20AC), a UV/vis detector (SPD-20A) and a column oven (CTO-20AC). The column used was a C18 (250 mm × 4.6 mm, 5 μm, Thermo) and the temperature was set to 35 °C. The mobile phase was acetonitrile/buffer (pH 4.5) 60/40 (v/v) and the flow rate was set to 1.2 mL/min. The drug was detected at 210 nm.

3. Results and discussion

3.1. Characterization of the prepared blends

Carrageenans are linear polymers of about 25,000 galactose derivatives with regular but imprecise structures, depending on the source and extraction conditions. XRD patterns of neat carrageenans showed a wide broad peak that corresponds to the amorphous state (Fig. 3). XRD patterns of the carrageenans blend also showed broad peaks indicating that the physical state of carrageenans was not altered during solvent evaporation mixing.

All prepared blends (κ/λ, κ/ι and ι/λ) and all compositions were transparent indicating that blends were miscible. In order to conclude if carrageenans form miscible or immiscible blends differential scanning calorimetry (DSC) was initially used to study the polymer miscibility.

Even though all samples were completely amorphous, no glass transition temperature (T_g) was recorded with DSC during heating from −60 to 80 °C (data not shown). According to Mitsuiki, Yamamoto, Mizuno, and Motoki (1998) T_g values of carrageenans are difficult to detected due to their small heat capacity change (ΔC_p) at the glass transition, even when a high sensitivity DSC is used. Picker et al. has also reported that carrageenans' T_g is near

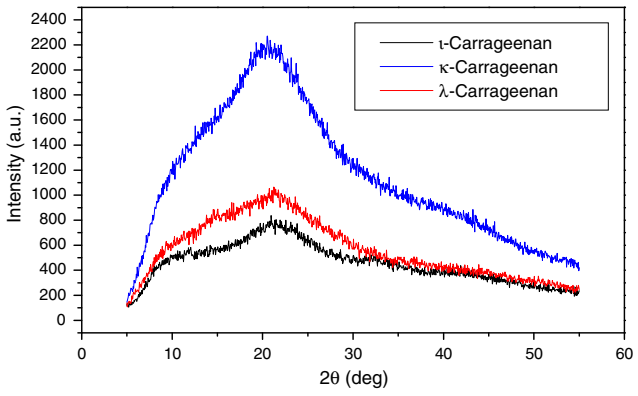

Fig. 3. XRD patterns of neat ι-, κ- and λ-carrageenans.

0 °C (Picker, 1999a, 1999b, 1999c). Thus, DSC proved inadequate to evaluate the miscibility of the carrageenans' blends and SEM had to be used.

Surface examination of the liquid nitrogen fractured blends with SEM revealed that the blends' morphology was depended by the composition. Small spheres scattered on the surface of the samples existed in all blends (Figs. 4–6) indicating that carrageenans in the blends were not miscible. Instead, the blends consisted of two different phases, with the small spheres being the dispersed phase and, thus, the blends were not miscible. The different coil–helix transition temperature of carrageenans in solution may explain the 'non-miscibility' finding due to which, it was not possible for carrageenans to form a hybrid helix that would correspond to a totally homogenous blend. κ/ι polymer blends' immiscibility is in accordance with Parker, Brigand, Minou, Trespoey, and Valle (1993) who observed a two-step gelation at κ/ι gels, with ι-carrageenan forming gel first and κ-carrageenan ensuing. It seems that even thought carrageenans have similar chemical structures it is not possible to form miscible blends. However, since the 'dispersed phase spheres' are smaller than 1 μm, the blends maybe compatible, most probably due to the weak interactions taking place between the reactive groups of carrageenans.

In order to evaluate the strength of the interactions between the different carrageenans while in solid form, the FT-IR spectra of the blends were recorded. As seen in Fig. 7 the main characteristic bands of carrageenans are located at 3500–3000 cm^{-1} (O—H stretching), 1290–1250 cm^{-1} (O=S=O asymmetric stretching), 1190 cm^{-1} (S=O symmetric stretching), 1160–1150 cm^{-1} (C—O—C asymmetric stretching), 1090–1060 cm^{-1} (S—O symmetric stretching), 1030–1050 cm^{-1} (C—O and C—OH stretching), 920–930 cm^{-1} (C—O—C stretching in 3,6-anhydrogalactose) and 845 cm^{-1} (C—O—S) stretching in a (1–3)-D-galactose (Prado-Fernandez, Rodriguez-Vazquez, Tojo, & Andrade, 2003; Sekkal & Legrand, 1993). By examining the wavenumbers of those peaks it can be seen that their position remained almost the same in all prepared blends and only the hydroxyl groups along with the sulfonic groups could have possible interacted. However, FT-IR spectra gave no solid proof that hydrogen bonds were formed between the two

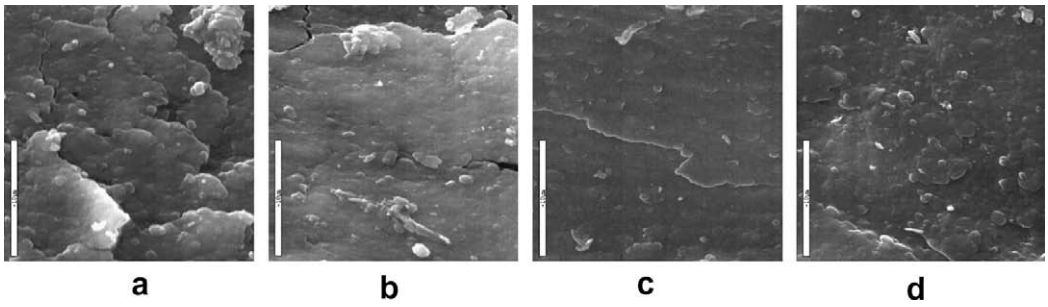

Fig. 4. SEM micrograph of liquid nitrogen fractured surfaces of ι/λ carrageenan blends having compositions: (a) 20/80, (b) 40/60, (c) 60/40 and (d) 80/20 w/w (bars are 10 μm).

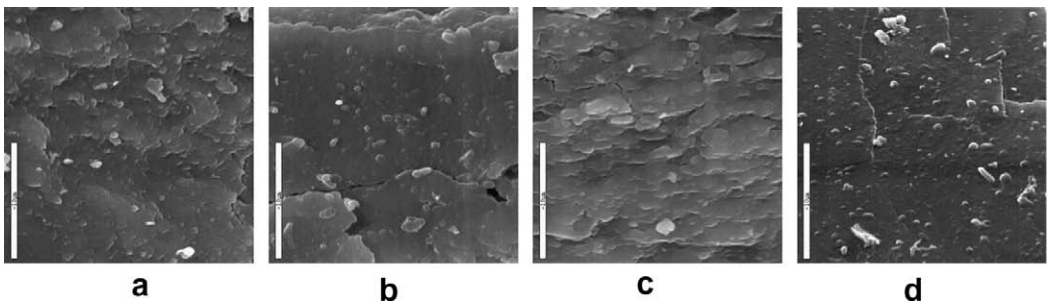

Fig. 5. SEM micrograph of liquid nitrogen fractured surfaces of κ/λ carrageenan blends having compositions: (a) 20/80, (b) 40/60, (c) 60/40 and (d) 80/20 w/w (bars are 10 μm).

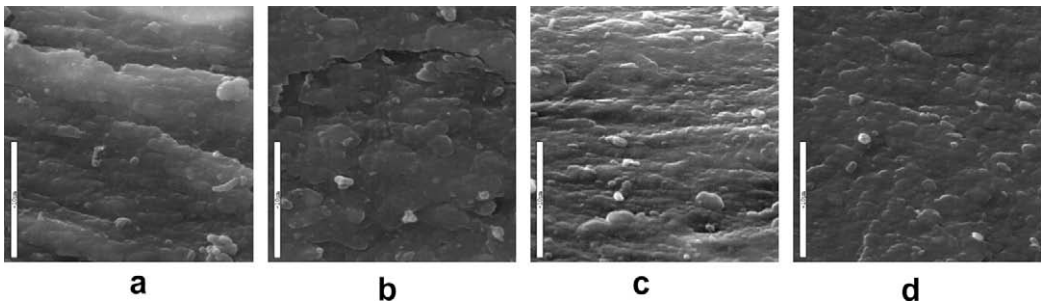

Fig. 6. SEM micrograph of liquid nitrogen fractured surfaces of κ/ι carrageenans blends having compositions: (a) 20/80, (b) 40/60, (c) 60/40 and (d) 80/20 w/w (bars are 10 μm).

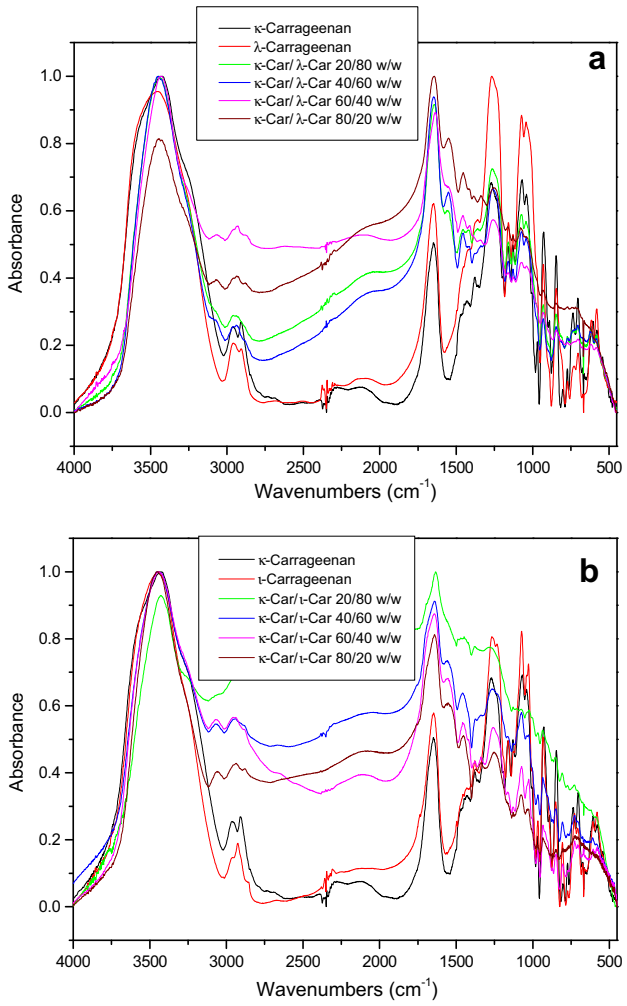

Fig. 7. FT-IR spectra of (a) κ/λ and (b) κ/ι carrageenan blends at different compositions.

carrageenans during the solvent evaporation procedure, either because they have not or because both intramolecular and intermolecular hydrogen bonds coexisted in the pure polymers and it was not possible to record any shift in the blends (Stolz & Cerezo, 2003).

Immiscibility is not unusual in polymer blends. In order to prepare miscible blends the free energy of mixing should be negative. However in some blends due to solvent effect strong interactions can form in polymer solutions. Such interactions may alter the properties of the blends used as drug carriers and the release rate of the drug. In order to elucidate the existence of such interactions in solutions, the miscibility of carrageenans was studied using a model based on viscosity measurements of the blends suggested by Chee (1990). According to this model, when two polymers are mixed in different weight fractions w_1 and w_2, the interaction parameter is expressed as ΔB and can be calculated from the following equation:

$$\Delta B = \frac{b - \bar{b}}{2w_1w_2} \quad (1)$$

where $\bar{b} = w_1b_{11} + w_2b_{22}$ b_{11} and b_{22} are the slopes of the viscosity curves for the pure components. b is related to Huggins' coefficient K_H and to the intrinsic viscosity $[\eta]$ as follows:

$$b = K_H[\eta]^2 \quad (2)$$

For a ternary system b is given by the equation:

$$b = w_1^2b_{11} + w_2^2b_{22} + 2w_1w_2b_{12} \quad (3)$$

b_{12} is the slope of the viscosity curve for the blend solution.

Chee has also suggested a more secure interaction parameter, μ, in case $[\eta]_1$ and $[\eta]_2$ are apart. The corresponding equation is:

$$\mu = \frac{\Delta B}{([\eta]_2 - [\eta]_1)^2} \quad (4)$$

$[\eta]_1$ and $[\eta]_2$ are the intrinsic viscosities for the pure component solutions. According to Chee, if $\mu \geqslant 0$ the polymers in the blend are miscible in the blend and if $\mu < 0$ the polymers are immiscible.

Sun, Wang, and Feng (1992) suggested a better equation for the definition of polymer miscibility:

$$\alpha = K_m - \frac{K_1[\eta]_1^2w_1^2 + K_2[\eta]_2^2w_2^2 + 2\sqrt{K_1K_2}[\eta]_1[\eta]_2w_1w_2}{([\eta]_1w_1 + [\eta]_2w_2)^2} \quad (5)$$

K_1, K_2 and K_m are the Huggins' constants for the individual components 1 and 2 and for the blend. If $a \geqslant 0$, the polymers in the blend are miscible and if $a < 0$ they are not (Basavaraju, Demappa, & Rai, 2006, 2007; Jayaraju, Basavaraju, Keshavayya, & Rai, 2006; Jayaraju, Raviprakash, Keshavayya, & Rai, 2006; Prashantha, Vasanth Kumar Pai, & Sherigara, 2004; Yichun et al., 2007). In order to calculate those parameters the relative viscosities of the blends were measured using different polymer ratios. For the pure carrageenans and for each polymer blend, five different concentrations were used 0.1, 0.2, 0.3, 0.4 and 0.5 wt.%. In Fig. 8, the relationship between reduced viscosity of neat polymers and different carrageenan blends has been plotted. A linear relationship between the two factors existed for all blends and for concentrations up to 0.3%. However, in some λ/ι and ι/κ blends and at concentrations 0.4 and 0.5 wt.%, a sharp increase of viscosity can be seen for blends containing high amounts of ι-carrageenan.

The intrinsic viscosity values for all blends and for all polymer ratios were calculated and presented in Fig. 9. The intrinsic viscosity values of all blends lie somewhere within the range of values of the pure components, apart from 80/20 w/w and 70/30 w/w κ/λ blends and the 10/90 w/w κ/ι blend, exhibiting lower viscosity values compared to the pure components, which might indicate a viscous synergism. Hernandez et al. (2001) measured the viscosity of κ- and λ-carrageenan alone and in mixtures with locust bean gum and attributed the lower viscosity in the mixture to a viscous synergism. However, in the present study viscosity values of the three blends are only slightly lower than the values of the pure components and thus not significant enough to draw a safe conclusion. Another observation is that λ-carrageenan has the highest viscosity, as expected, given its known ability to interact with polar solvents like water. Finally, ι-carrageenans with the two sulfonic groups on its repeating unit, has slightly higher viscosity than κ-carrageenan.

The interaction parameters μ and α were calculated from intrinsic viscosity values using the Chee and Sun equations (Table 1). Both interaction parameters were always <0 providing another proof that the carrageenans formed immiscible blends (SEM micrograph also revealed that carrageenans form different phases during mixing).

3.2. Carrageenans/Tolterodine L-Tartrate formulations

The primary goal of the present study was to prepare controlled release formulations of Tolterodine. Fig. 10 shows Tolterodine's release rate from solid dispersion formulations prepared with one type of carrageenan each time. In formulations prepared with ι- and κ-carrageenan, Tolterodine is released within an hour while the rate is slower in formulations prepared with λ-carrageenans. According to Picker (1999a, 1999b, 1999c) the higher swelling

capacity of κ-carrageenan led to a higher release rate for diclofenac sodium drug from formulations containing κ-carrageenan compared to formulations containing ι-carrageenan. However, such a behaviour was not observed with Tolterodine's release in the present study. Another remarkable observation is that although the pellet was completely disintegrated after 12 h, only 75% of the drug was dissolved at the most. Possibly, strong interactions between Tolterodine and carrageenans prevented Tolterodine from being totally released.

Although Tolterodine L-Tartrate is a slightly water soluble drug, its fast dissolution has to be attributed either to the hydrophilic character of the carriers or to the amorphous state of the drug (Kanaze et al., 2006; Karavas, Georgarakis, Docoslis, & Bikiaris, 2007; Karavas, Georgarakis, Sigalas, Avgoustakis, & Bikiaris, 2007; Leuner & Dressman, 2000; Papageorgiou et al., 2006). Solid dispersion has been used for this purpose i.e. is a technique widely used to improve dissolution rate through amorphization (Karavas, Georgarakis, Docoslis et al., 2007; Karavas, Georgarakis, Sigalas et al., 2007; Papageorgiou, Docoslis, Georgarakis, & Bikiaris, 2009). The amorphization is attributed to strong interactions taking place between the drug and the polymer carrier (Karavas, Georgarakis, & Bikiaris, 2006). Fig. 11 shows XRD patterns of solid dispersions of Tolterodine in λ-carrageenan in four different concentrations. As can be seen a wide peak was found for each formulation but no characteristic peak of Tolterodine was recorded. The wide peak most probably corresponds to amorphous Tolterodine. To verify this hypothesis FT-IR spectra of solid dispersions were generated (Fig. 12).

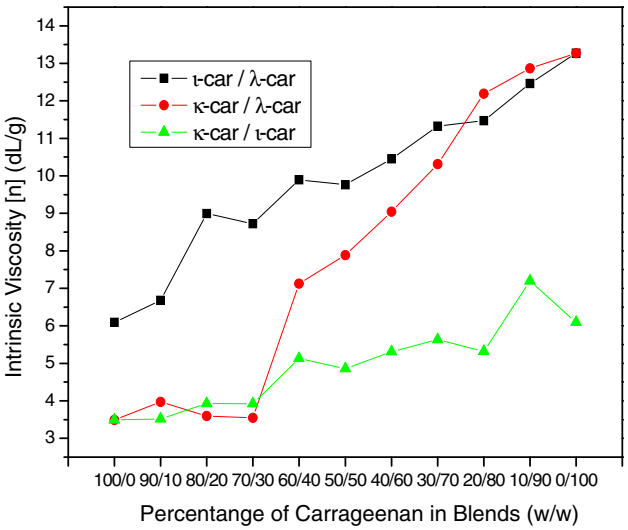

Fig. 9. Intrinsic viscosity values of various carrageenan blends.

The sharp peak at 3600 cm^{-1} in Tolterodine's FT-IR spectra corresponds to the —OH group of the drug and indicates that those

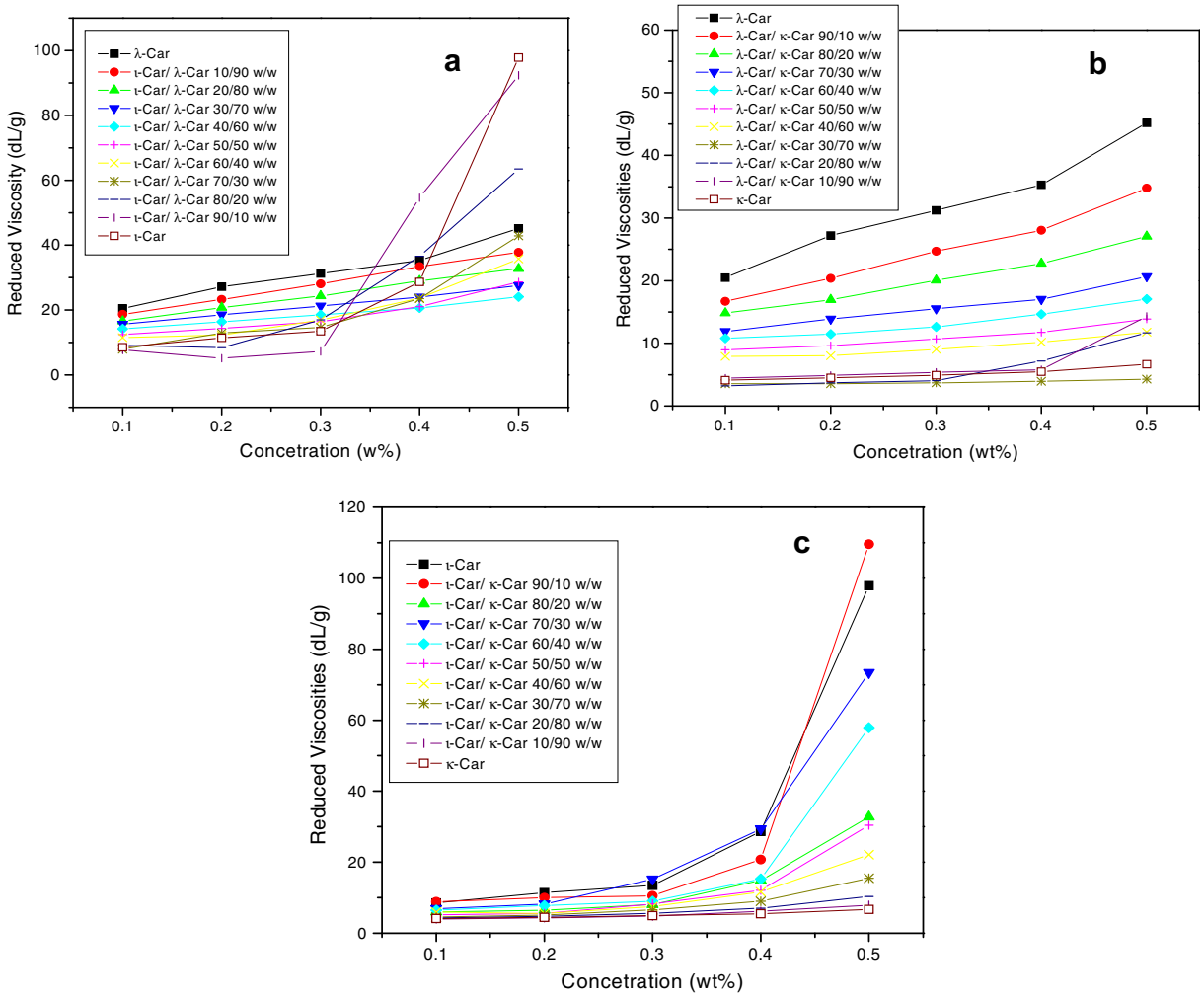

Fig. 8. Plots of reduced viscosities toward blends concentration: (a) λ/ι blends, (b) λ/κ blend and (c) ι/κ blends.

Table 1
Miscibility parameters μ and α of carrageenan blends.

Composition of carrageenan blends (w/w)	ι/λ-Carrageenans		κ/λ-Carrageenans		κ/ι-Carrageenans	
	μ	α	μ	α	μ	α
10/90	−37.1	−0.01	−12.21	−0.05	−12.21	−0.26
20/80	−37.1	0.03	−12.21	−0.06	−12.21	−0.01
30/70	−37.1	−0.02	−12.21	−0.01	−12.21	−0.03
40/60	−37.11	−0.02	−12.22	−0.03	−12.21	0
50/50	−37.11	−0.04	−12.22	−0.01	−12.23	−0.14
60/40	−37.1	−0.15	−12.22	−0.04	−12.22	−0.14
70/30	−37.11	−0.09	−12.22	0.26	−12.22	−0.02
80/20	−37.1	−0.27	−12.21	0.08	−12.22	−0.14
90/10	−37.1	−0.11	−12.21	−0.07	−12.21	−0.11

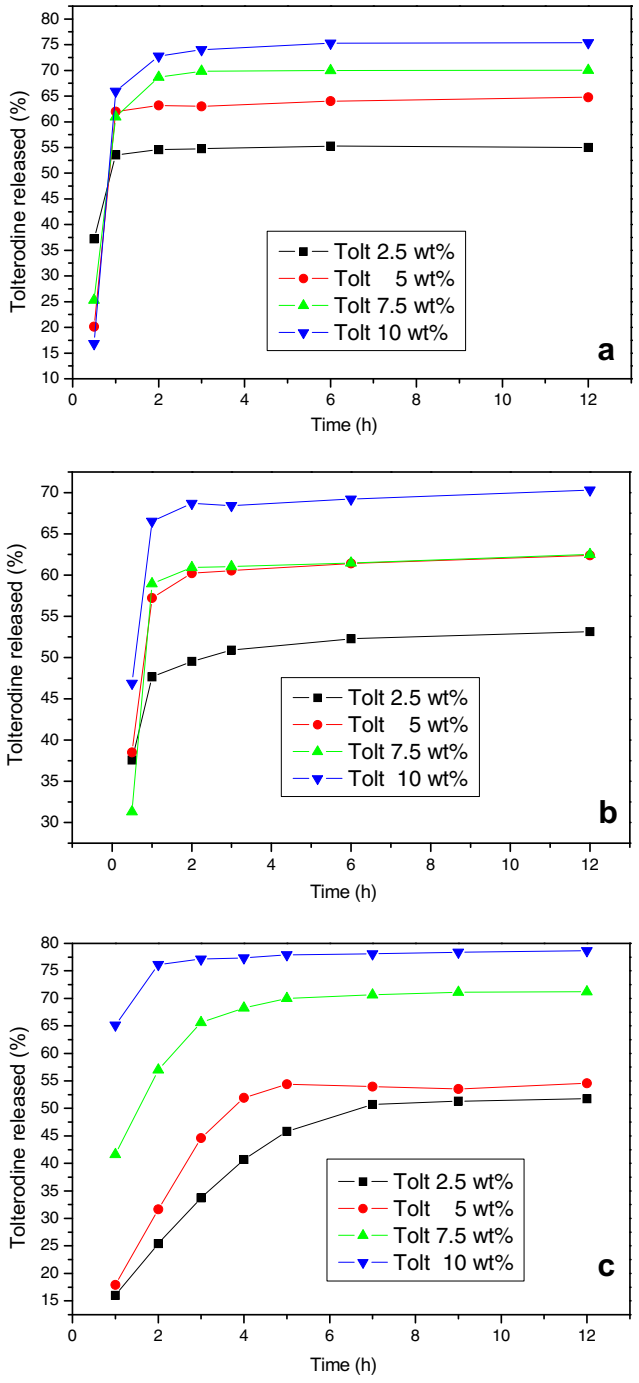

Fig. 10. Tolterodine's release from solid dispersions prepared by solvent evaporation technique: (a) ι-carrageenan (b) κ-carrageenan and (c) λ-carrageenan.

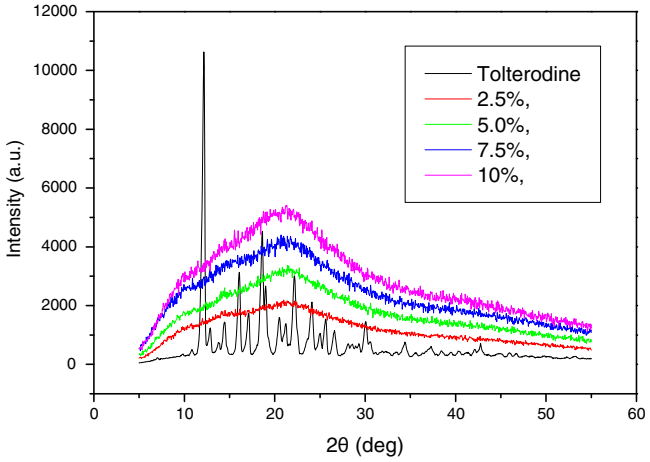

Fig. 11. XRD patterns of solid dispersions of Tolterodine to λ-carrageenan.

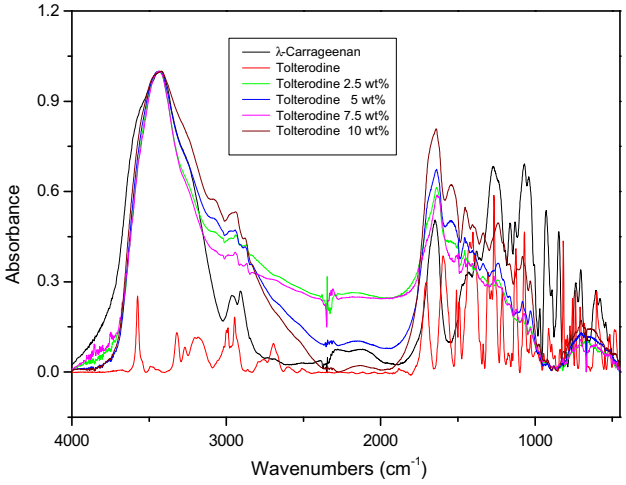

Fig. 12. FT-IR spectra of solid dispersions of Tolterodine to λ-carrageenan.

groups are uncoupled. That peak is not detected in the formulations spectra either because the broad peak of hydrogen absorption overlaps (Fig. 12) or because the —OH groups form hydrogen bonds with carrageenans' reactive groups. An examination of carrageenans sulfonic groups absorption supports the later explanation. Although sulfonic groups are supposed to absorb at 1272 cm^{-1}, in the solid dispersions their peak is recorded at 1238 cm^{-1} indicating that the groups participate in hydrogen bonding. Similar interactions between carrageenans and several different drugs have been reported in literature (Bonferoni, Rossi, Ferrari, Bettinetti et al. 2000; Bonferoni et al., 1993, 1994, 1998; Hariharan et al., 1997; Picker & Gabelick, 1997). Other characteristic shifts are those of the S—O symmetric group which in neat carrageenan is located at 1070 cm^{-1} while in the solid dispersions is shifted to 1081 cm^{-1}. On the top of that the absorption of the ≻C—OH group recorded at 1040 cm^{-1} remains unaffected, which is an indication that the hydroxyl groups of carrageenans have not participated in the hydrogen bonding.

To verify the hypothesis that the fast dissolution rate is attributed to Tolterodine's amorphization, physical mixtures of Tolterodine L-Tartrate and ι-carrageenan were also prepared and studied. As can be seen from the XRD patterns in Fig. 13 Tolterodine's peak at about $2\theta = 12°$ is present in all formulations and as the concentration of the drug increases so is the peak. This indicates that in physical mixtures the drug remains in crystalline state.

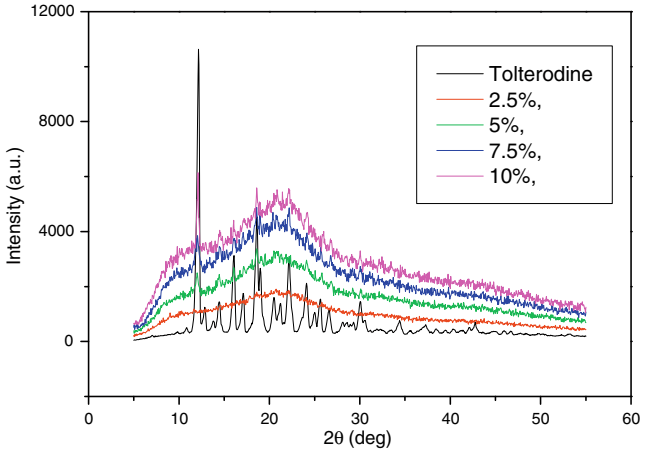

Fig. 13. XRD patterns of several ι-carrageenan/Tolterodine physical mixtures.

A slower release rate was observed in mixtures compared to solid dispersion formulation (Fig. 14). Physical mixtures of κ- and ι-carrageenans released the drug over a 4 h period while solid dispersions released the drug over a 1 h period. In formulations containing λ-carrageenan, the release lasted 12 h and seams to almost follow a zero order kinetic. Bonferoni, Rossi, Ferrari, Bettinetti et al. (2000) reported a similar release profile for diltiazem from pure λ-carrageenan. Although the drug's loading in the formulation was found to affect the release profile, the most pronounced observation is the different release rates of the drug from the formulations prepared with different carrageenan type.

Hydrophilic polymers that swell in aqueous media (such as carrageenans) have been widely used as excipients in controlled release tablets. One of their disadvantages is the rapid dissolution of the surface drug followed by a quick diffusion through the outer hydrated gel layer that causes a rapid initial release followed by a period of slower release as the diffusion path length increases due to the concomitant hydration and swelling when carrageenans being used as drug carriers (Gupta et al., 2001; Sakiyama, Chu, Fujii, & Yano, 1993). Among others, the release rate depends on the drug's hydrophobicity. The more hydrophobic the drug is, the stronger the adsorption in the chains, leading to lower diffusion coefficient (Coviello, Matricardi, Marianecci, & Alhaique, 2007; Makino, Idenuma, Murakami, & Ohshima, 2001; Sjoberg, Persson, & Caram-Lelham, 1999). However, in the present study the differences in release rates have been attributed to different physical properties of those polymers which influence their ability to interact with Tolterodine.

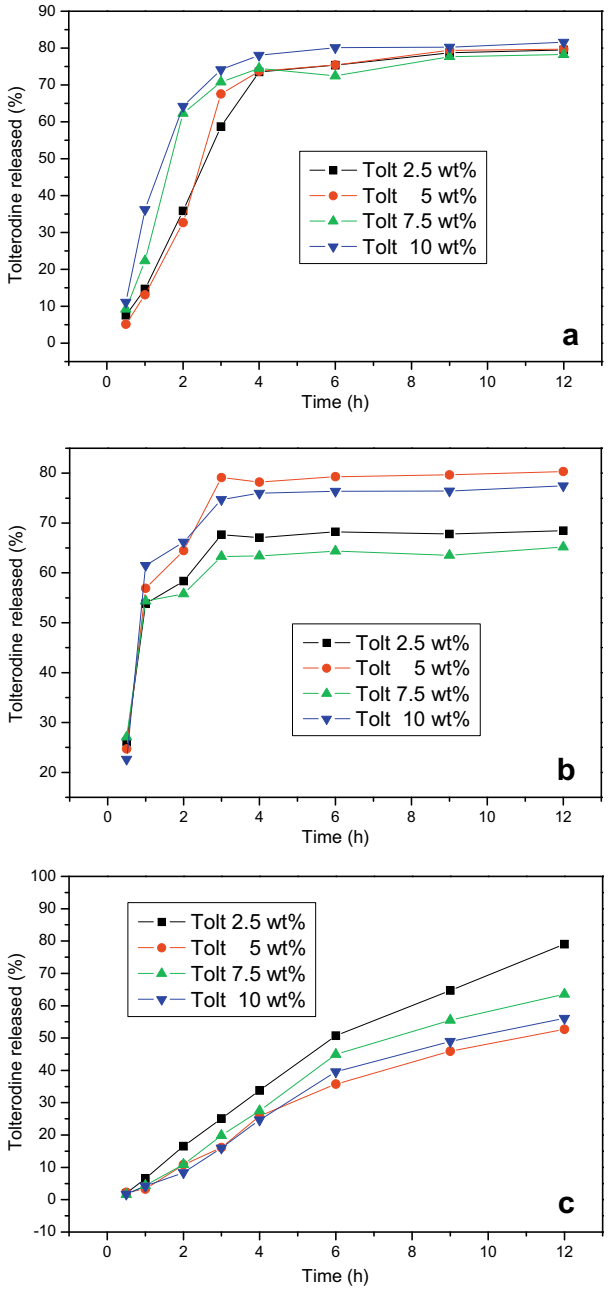

Fig. 14. Tolterodine's release from its physical mixtures with (a) ι-carrageenan, (b) κ-carrageenan and (c) λ-carrageenan.

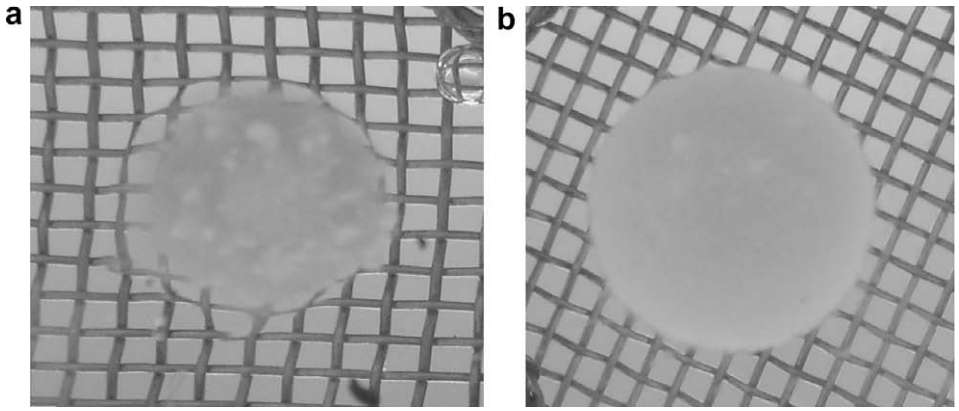

Fig. 15. Different tablets consisted by (a) κ-carrageenan and (b) λ-carrageenan after 3 h in the dissolution medium. κ-Carrageenan forms a gel while λ-carrageenan does not.

k- and ι-carrageenans are mainly made up of alternating 1,3-linked b-D-galactopyranose-4-sulfate and 1,4-linked 3,6-anhydro-D-galactopyranose units, containing different amounts of ester sulfate groups. At low temperatures these carrageenans follow a random coil conformation of double helices. Sulfate groups are located at the outside of the helix. Hydrogen bonds formed between the two chains are responsible for helix stabilization (Makino et al., 2001). In contact with an aqueous solution water penetrates the matrix and a hydrogel is formed (Fig. 15a). After that, drug is released due to erosion. Swelling and erosion happens concomitantly. λ-Carrageenan's behaviour is different since no surface gel is formed in aqueous environment (Fig. 15b). Previous studies have demonstrated that λ-carrageenan can interact strongly with basic drugs and that this interaction can be exploited in controlled release formulations, especially with very soluble drugs (Bonferoni, Rossi, Ferrari, Bettinetti et al., 2000; Bonferoni, Rossi, Ferrari, Stavik et al., 2000). In addition, the relevance of hydrophobic interactions in drug–polymer aqueous systems has already been demonstrated (Oliva et al., 2003). In the present study the interactions between Tolterodine and carrageenans play an important role.

3.3. Carrageenans blends and Tolterodine L-Tartrate formulations

As already shown, although physical mixtures of Tolterodine with carrageenans exhibited prolonged release, the kinetics were far from ideal when only one type of carrageenan was used. The use of a polymer blend instead of one polymer might be an improvement as it has been reported that the inter penetrating networks formed in the blends slows down the drugs' release rate (Bonferoni, Rossi, Ferrari, Bettinetti et al., 2000; Bonferoni, Rossi, Ferrari, Stavik et al., 2000; Kasapis & Al-Marhoobi, 2005; Michon et al., 1996; Ridout et al., 1996; Rodriguez-Hernandez & Tecante, 1999; Shumilina & Shchipunov, 2002; Tapia et al., 2004, 2005; Villanueva et al., 2004). A mixture of k-carrageenan with microcrystalline cellulose has been used to modulate tableting and release properties (Picker, 1999a) and the majority of the formulations prepared showed linear and sustained release profiles (Nerurkar, Jun, Price, & Park, 2005). Zero-order release profile has also been achieved by combining different carrageenans types (Hariharan et al., 1997) similar to the blends used in the present study. Fig. 16 displays Tolterodine's release rates from polymer blends having different carrageenan ratios. The drug's concentration was kept at 5% w/w and the formulations were always prepared by the solvent evaporation technique.

Tolterodine's rate of release from solid dispersions formulations made of carrageenan blends was slower compared to the release rate from solid dispersion formulations made of one carrageenan only (Figs. 10 and 16). Formulations consisted of ι/λ and κ/λ blends, released the drug over a 5 h period while formulations consisted by κ/ι blends released the drug over a 9 h period. However, the release seems to follow 1st order kinetic contrary to the release aimed in the present study. Since those formulations were prepared by solvent evaporation technique, 1st order release has to be attributed to the amorphization of the drug (amorphization was verified with XRD, data not shown), as was the case when the pure polymers were used (Fig. 11). Thus, physical mixtures of pure polymers with zero-order release kinetics are the formulation of choice (drug remains in crystalline state). For that reason physical mixtures of various polymer blends/drug proportions were prepared. The mixtures consisted from ι/λ carrageenans at ratios 20/80, 40/60 and 80/20 and drug concentrations of 2.5%, 5.0%, 7.5% and 10.0% were the most interesting (Fig. 17).

Zero-order release rates of ι/λ 20/80 w/w and 40/60 w/w blends has been achieved and thus those blends are ideal for controlled release systems. As the proportion of λ-carrageenan in the formulation was reduced the release followed 1st order kinetics. Apart from the crystalline state of the drug in physical mixtures, interactions between drug and carrageenans may also play an important role.

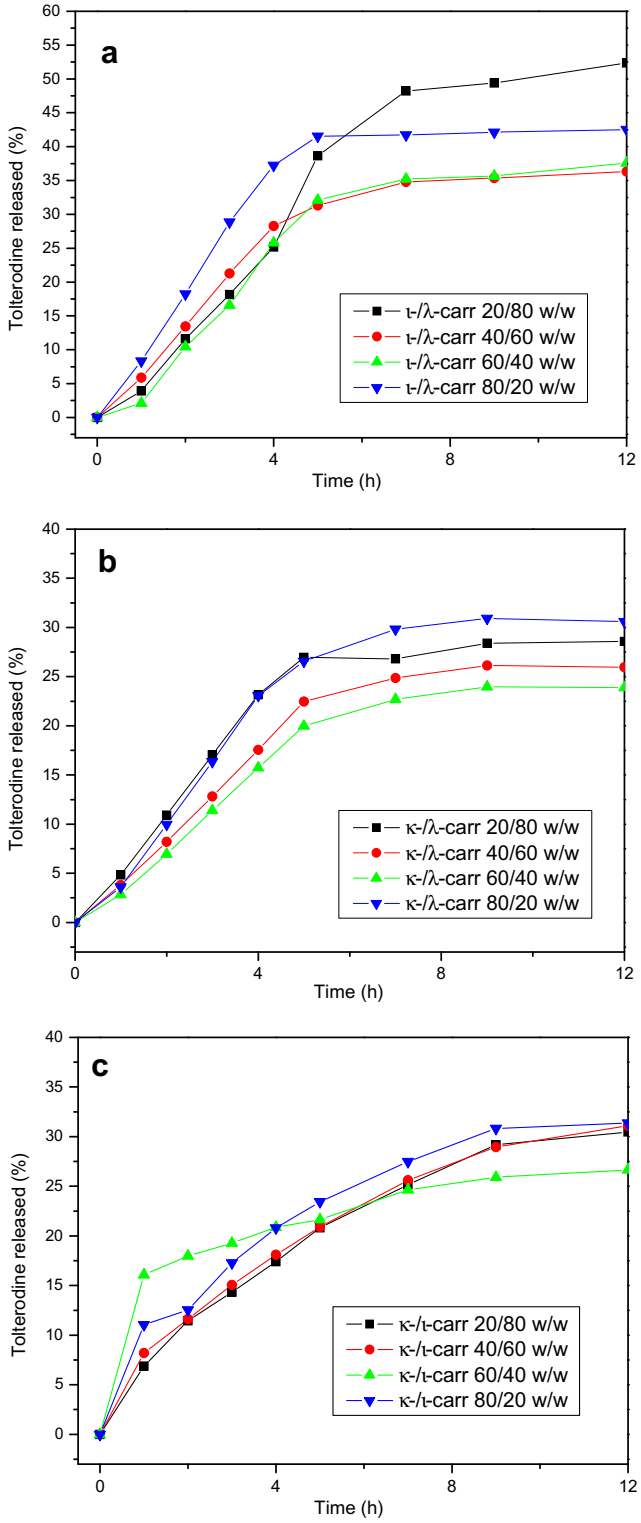

Fig. 16. Tolterodine's release from solid dispersions prepared by solvent evaporation technique: (a) ι-/λ-carrageenans blends, (b) κ-/λ-carrageenans blends and (c) κ-/ι-carrageenans blends.

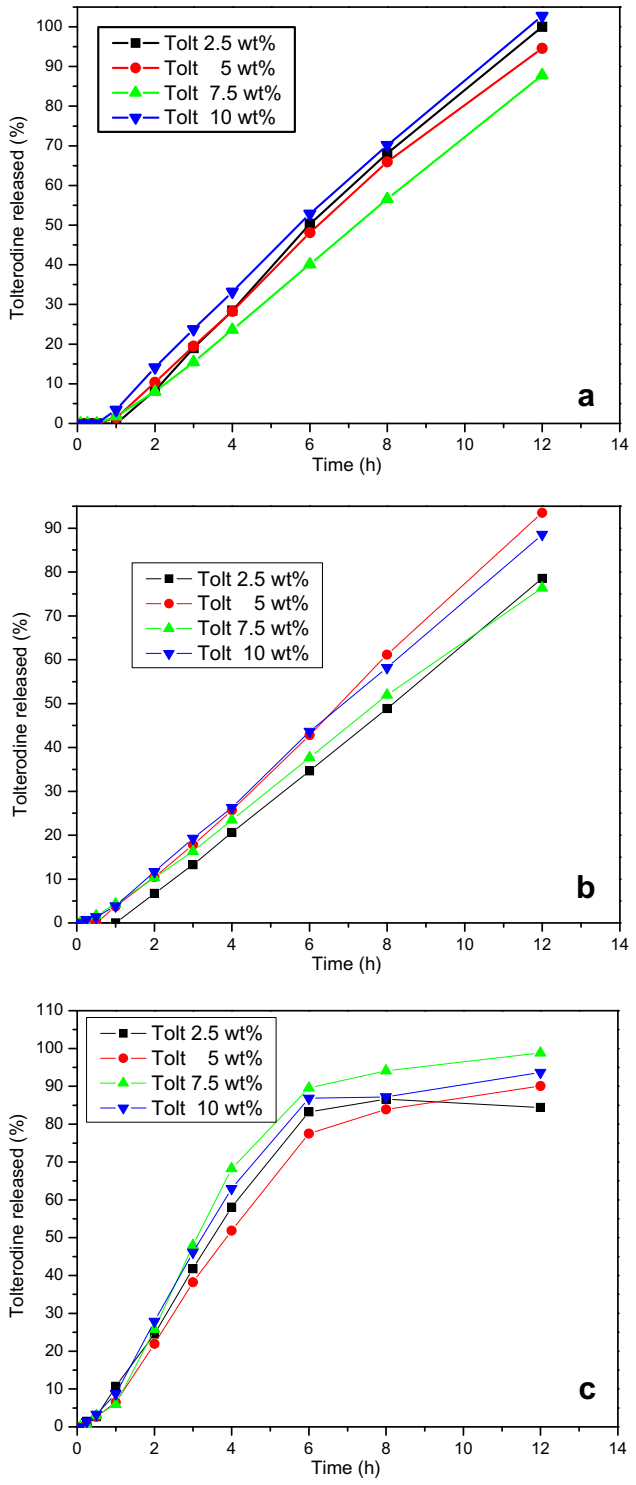

Fig. 17. Tolterodine's release from its physical mixtures with ι/λ-carrageenans blends: (a) 20/80 w/w, (b) 40/60 w/w, and (c) 80/20 w/w prepared by physical mixing.

4. Conclusions

Although ι-, κ- and λ-carrageenans cannot form miscible blends, they can still be used in the development of a controlled release Tolterodine L-Tartrate formulation, due to their ability to form hydrogen bonds with the drug.

From all the formulations that were prepared, either by solvent evaporation technique or by the physical mixture technique, only three formulations, i.e. (a) the physical mixture of Tolterodine with λ-carrageenan, (b) the physical mixture of Tolterodine with ι/λ carrageenan blend at 20/80 ratio and (c) the physical mixture of Tolterodine wit ι/λ carrageenan blend at 40/60 ratio, followed zero-order release kinetic. Thus, only these formulations can be used for the controlled release of Tolterodine L-Tartrate.

References

Basavaraju, K. C., Demappa, T., & Rai, S. K. (2006). Preparation of chitosan and its miscibility studies with gelatin using viscosity, ultrasonic and refractive index. *Carbohydrate Polymers, 66*, 357–362.

Basavaraju, K. C., Demappa, T., & Rai, S. K. (2007). Miscibility studies of polysaccharide xanthan gum and Peo (polyethylene oxide) in dilute solution. *Carbohydrate Polymers, 69*, 462–466.

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., 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*(2) [article 15].

Bonferoni, M. C., Rossi, S., Tamayo, M., Pedraz, J. L., Dominguez-Gil, A., & Caramella, C. (1993). On the employment of lambda-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 lambda-carrageenan in a matrix system. II. Lamda-carrageenan and hydroxypropylmethycellulose mixtures. *Journal of Controlled Release, 30*, 175–182.

Bonferoni, M. C., Rossi, S., Tamayo, M., Pedraz, J. L., Dominguez-Gil, A., & 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.

Chee, K. K. (1990). Determination of polymer–polymer miscibility by viscometry. *European Polymer Journal, 26*, 423–426.

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

Gupta, V. K., Hariharan, M., Wheatley, T. A., & Price, J. C. (2001). Controlled-release tablets from carrageenans: Effect of formulation, storage and dissolution factors. *European Journal of Pharmaceutics and Biopharmaceutics, 51*, 241–248.

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.

Hernandez, M. J., Dolz, J., Dolz, M., Delegido, J., & Pellicer, J. (2001). Viscous synergism in carrageenans (κ and λ) and locust bean gum mixtures: Influence of adding sodium carboxymethylcellulose. *Food Science and Technology International, 7*(5), 383–391.

Jayaraju, J., Basavaraju, K. C., Keshavayya, J., & Rai, S. K. (2006). Viscosity, ultrasonic and refractometric studies of chitosan/polyethylene glycol blend in solution at 30, 40 and 50 °C. *Journal of Macromolecular Science, Part B: Physics, 45*, 741–751.

Jayaraju, J., Raviprakash, S. D., Keshavayya, J., & Rai, S. K. (2006). Miscibility studies on chitosan/hydroxymethylcellulose blend in solution by viscosity, ultrasonic velocity, density and refractive index methods. *Journal of Applied Polymer Science, 120*, 2738–2742.

Kanaze, F. I., Kokkalou, E., Niopas, I., Georgarakis, M., Stergiou, A., & Bikiaris, D. (2006). Novel drug delivery systems for flavonoid compounds with enhanced solubility based on solid dispersions with polyvinylpyrolidone and polyethyleneglycol. *Journal of Applied Polymer Science, 102*, 460–471.

Karavas, E., Georgarakis, E., & Bikiaris, D. (2006). Felodipine nanodispersions as active core for predictable pulsatile chronotherapeutics using PVP/HPMC blends as coating layer. *International Journal of Pharmaceutics, 313*, 189–197.

Karavas, E., Georgarakis, M., Docoslis, A., & Bikiaris, D. (2007). Combining SEM, TEM, and micro-Raman techniques to differentiate between the amorphous molecular level dispersions and nanodispersions of a poorly-water soluble drug within a polymer matrix. *International Journal of Pharmaceutics, 340*, 76–83.

Karavas, E., Georgarakis, E., Sigalas, M. P., Avgoustakis, K., & Bikiaris, D. (2007). Investigation of the release mechanism of a sparingly water-soluble drug from solid dispersions in hydrophilic carriers based on physical state of drug, particle size distribution and drug–polymer interactions. *European Journal of Pharmaceutics and Biopharmaceutics, 66*, 334–347.

Kasapis, S., & Al-Marhoobi, I. M. (2005). Bridging the divide between the high- and low-solid analyses in the gelatin/κ-carrageenan mixture. *Biomacromolecules, 6*, 14–23.

Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *European Journal of Pharmaceutics and Biopharmaceutics, 50*, 47–60.

Makino, K., Idenuma, R., Murakami, T., & Ohshima, H. (2001). Design of a rate- and time-programming drug release device using a hydrogel: Pulsatile drug release from k-carrageenan hydrogel device by surface erosion of the hydrogel. *Colloids and Surfaces B: Biointerfaces, 20*, 355–359.

Michon, C., Cuvelier, G., Launay, B., & Parker, A. (1996). Viscoelastic properties of ι-carrageenan/gelatin mixtures. *Carbohydrate Polymers, 31*, 161–169.

Mitsuiki, M., Yamamoto, Y., Mizuno, A., & Motoki, M. (1998). Glass transition properties of water content for various low-moisture galactans. *Journal of Agricultural and Food Chemistry, 46*, 3528–3534.

Moffat, A. C., Osslton, M. D., Widdop, B., & Galichet, L. Y. (2004). *Clarke's analysis of drugs and poisons*. London: Pharmaceutical Press [Electronic version].

Nakano, M., & Ogata, A. (1984). Examination of natural gums as matrices for sustained release of theophylline. *Chemical and Pharmaceutical Bulletin, 32*, 782–785.

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.

Oliva, M., Díez-Pérez, I., Gorostiza, P., Lastra, C. F., Oliva, I., Caramella, C., et al. (2003). Self-assembly of drug–polymer complexes: A spontaneous nanoencapsulation process monitored by atomic force microscopy. *Journal of Pharmacological Science, 92*(1), 77–83.

Papageorgiou, G. Z., Bikiaris, D., Karavas, E., Politis, S., Docoslis, A., Park, Y., et al. (2006). Effect of physical state and particle size distribution on dissolution enhancement of Nimodipine/PEG solid dispersions prepared by melt mixing and solvent evaporation. *AAPS Journal, 8*, E623–E631.

Papageorgiou, G. Z., Docoslis, A., Georgarakis, M., & Bikiaris, D. (2009). The effect of physical state on the drug dissolution rate. Miscibility studies of Nimodipine with PVP. *Journal of Thermal Analysis and Calorimetry, 95*, 903–915.

Parker, A., Brigand, G., Minou, C., Trespoey, A., & Valle, P. (1993). Rheology and fracture of mixed ι- and κ-carrageenan gels: Two-step gelation. *Carbohydrate Polymers, 20*, 253–262.

Picker, K. M. (1999a). The use of carrageenan in mixture with microcrystalline cellulose and its functionality for making tablets. *European Journal of Pharmaceutics and Biopharmaceutics, 48*, 27–36.

Picker, K. M. (1999b). Matrix tablets of carrageenans I. A compaction study. *Drug Development and Industrial Pharmacy, 25*(3), 329–337.

Picker, K. M. (1999c). Matrix tablets of carrageenans II: Release behavior and effect of added cations. *Drug Development and Industrial Pharmacy, 25*, 339–346.

Picker, K. M., & Gabelick, C. (1997). Tablets of carrageenans with theophylline. *Proceedings of the Controlled Release Society, 24*, 235–236.

Prado-Fernandez, J., Rodriguez-Vazquez, J. A., Tojo, E., & Andrade, J. M. (2003). Quantitation of κ-, ι- and λ-carrageenans by mid-infrared spectroscopy and PLS regression. *Analytica Chimica Acta, 480*, 23–37.

Prashantha, K., Vasanth Kumar Pai, K., & Sherigara, B. S. (2004). Studies on the miscibility of poly(2-hydroxyethylmethacrylate) and hydroxypropyl methyl cellulose blends. *International Journal of Polymeric Materials, 53*, 499–506.

Ridout, M. J., Garza, S., Brownsey, G. J., & Morris, V. J. (1996). Mixed iota–kappa gels. *International Journal of Biological Macromolecules, 18*, 5–8.

Rodriguez-Hernandez, A. I., & Tecante, A. (1999). Dynamic viscoelastic behavior of gellan-ι-carrageenan and gellan-xanthan gels. *Food Hydrocolloids, 13*(1), 59–64.

Sakiyama, T., Chu, C.-H., Fujii, T., & Yano, T. (1993). Preparation of polyelectrolyte complex gel from chitosan and *k*-carrageenan and its pH-sensitive swelling. *Journal of Applied Polymer Science, 50*, 2021–2025.

Sekkal, M., & Legrand, P. (1993). A spectroscopic investigation of the carrageenans and agar in the 1500–100 cm^{-1} spectral range. *Spectrochimica Acta A, 49*(2), 209–221.

Shumilina, E. V., & Shchipunov, Yu. A. (2002). Chitosan–carrageenan gels. *Colloid Journal, 64*(3).

Sjoberg, 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.

Stolz, C. A., & Cerezo, A. S. (2003). MM3 potential energy surfaces of trisaccharides. II. Carrageenan models containing 3,6-anhydro-D-galactose. *Biopolymers, 70*, 227–239.

Sun, Z., Wang, W., & Feng, Z. (1992). Criterion of polymer–polymer miscibility determined by viscometry. *European Polymer Journal, 28*, 1259–1261.

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., Basuato, C., et al. (2004). Comparative studies on polyelectrolyte complexes and mixtures of chitosan–alginate and chitosan–carrageenan as prolonged diltiazem chlorohydrate release systems. *European Journal of Pharmaceutics and Biopharmaceutics, 57*, 65–75.

van de Velde, I. F., & De Ruiter, G. A. (2005). Carrageenan. In A. Steinbuchel & R. H. Marchessault (Eds.), *Biopolymers for medical and pharmaceutical applications*. Willey-VCH.

Villanueva, R. D., Mendoza, W. G., Rodrigueza, M. R. C., Romero, J. B., & Montano, M. N. E. (2004). Structure and functional performance of gigantinacean kappa–iota hybrid carrageenan and solieriacean kappa–iota carrageenan blends. *Food Hydrocolloids, 18*, 283–292.

Yichun, Y., Weihua, D., Rui, Z., Hai, L., Nianhua, D., Linbo, G., et al. (2007). Miscibility studies on the blends of collagen/chitosan by dilute solution viscometry. *European Polymer Journal, 43*, 2066–2071.