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Synthesis and characterization of hydrogels formed from a glycidyl methacrylate derivative of galactomannan

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Abstract

The present investigation describes a procedure for the synthesis of a glycidyl methacrylated derivative from galactomannan, GA-MA, and the respective hydrogel formation. The galactomannan (GA), raw material, was purified and dissolved in DMSO. After dissolution, 4-dimethyl-amino-pyridine (DMAP) and glycidyl methacrylate (GMA) were added. The modified polymer, quoted as GA-MA, was purified by precipitation in ethanol. Hydrogels were obtained from GA-MA in aqueous solution by polymerization of GA-MA using sodium persulfate (SP), as initiator, and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED), as catalyst. For this, the cross-linking process was trigged by the addition of TEMED and sodium persulfate aqueous solutions. Two different concentrations of TEMED and SP were used. GA, GMA and GA-MA were characterized by FT-IR and NMR (^{13}C and ^{1}H) spectroscopy. The addition of GMA on GA molecules was confirmed through FT-IR results by appearing of a band at $\nu = 1717\,\mathrm{cm}^{-1}$ and also by the cleavage of C=C groups of GA-MA (band at $\nu = 1636\,\mathrm{cm}^{-1}$) during the cross-linking process. The signals attributed to vinyl carbon of methacrylate (δ 138.52, 130.06 ppm), to carbonyl (δ 171.87 ppm) and to methyl group (δ 20.19 ppm) were observed in the ^{13}C NMR spectra of GA-MA. The addition of methacrylate on GA was also confirmed through the signals present in ^{1}H NMR spectra of GA-MA. The formation of hydrogel was observed by complete gelation. The hydrogels were characterized by FT-IR and by measuring the equilibrium water content (EWC) in pH = 7.0 and 1.0. The hydrogels contain 83 wt.% of water at 25 °C and 85 wt.% at 37 °C. Good resistance to degradation in acidic conditions, pH = 1.0, was observed at 37 °C up to 48 h. These properties suggest that the GA-MA hydrogels may be a new material for pharmaceutical use, mainly for drug delivery system.

Keywords: Galactomannan; Glycidyl methacrylate; Hydrogel synthesis; Characterization

1. Introduction

In the past, gums were largely used as plant exudates. Most plant families have species that exude gums to some degree. The exudates may contain mixtures of polysaccharides. Polysaccharides have been widely used in pharmaceutical drug delivery systems, either as natural materials or as derivatives compounds, because of their low toxicity, specific biodegradability, high stability and low cost. Biodegradable polymers are frequently used in delivery systems as coating material for solid dosage forms (Cavalcanti et al., 2002) or as drug-loaded hydrogels (Peppas et al., 2000). Hydrogels may be natural or semi-synthetic materials and are considered attractive

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for delivery systems of a large variety of pharmaceutically active drugs, drug peptides and proteins. Galactomannans (GA) are polysaccharides obtained from exudates or seeds of different vegetable species. They have been employed in research activities as pharmaceutical matrices, especially for drug delivery systems (Sinha and Kumria, 2001). The cross-linking of polysaccharides is somewhat important in pharmaceutical field because it increase the mechanical properties of the hydrogels without to affect, in severe degree, the biodegradability. The chemical modification of galactomannan, obtained from *Prosopis juliflora*, by reaction with glycidyl methacrylate (GMA) and further synthesis of the hydrogel is described in this report. The characterization of raw materials, intermediate product and hydrogel are presented and discussed.

2. Materials and methods

2.1. Materials

Exudate of *P. juliflora* was kindly supplied by (Embrapa/Petrolina, PE, Brazil). GMA (Acros, 15895000), sodium persulfate (SP, Sigma, 216232), 4-dimethyl-amino-pyridine (DMAP, Aldrich, 552821), dimethyl sulfoxide (DMSO, Labsynt, Brazil), and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED, Sigma, 2037446) were used with no further purification. For NMR analysis the D_2O (99.96 at.% D) was supplied by Isotec Inc., Matheson®, USA.

2.2. Equipments

Infrared spectra were obtained on a Bomem FT-IR model MB100 spectrometer. To achieve a $2\,cm^{-1}$ on resolution, 128 scans were performed in each spectrum.

All ^{13}C and ^{1}H NMR spectra were obtained on a Varian spectrometer, model Oxford 300 operating at 300 MHz. Solutions of GA and GA-MA ($150\,mg\,ml^{-1}$ in concentration) were prepared in D_2O. The angle pulse and the relaxation time used to obtain the ^{1}H NMR spectra were fixed in 90° and 30 s, respectively. The signal relative to water was suppressed by irradiation during the relaxation. For the ^{13}C NMR, pulse angle and the relaxed time were, respectively, 30° and 1 s. The temperature of sample in the NMR experiments was maintained in 60 °C. Tetramethylsilane (TMS) was used as intern reference. The chemical shift was given in ppm.

The GC-MS analysis was used to detect the presence of glycidol (an by-product of reaction of GA and GMA). It was performed on a Shimadzu gas chromatograph coupled with a mass selective detector model QP2000A. The GC column was a capillary Carbowax 60 (60 m length, 0.25 mm diameter). The injection temperature was set at 100 °C (during 6 min) and then changed to 200 °C at a heating rate of $5\,°C\,min^{-1}$.

The average molecular weight of GA was determined using a HPLC Shimadzu, equipped with an Ultrahydrogel linear column and refraction index as detector. The solvent was $NaNO_3$ 0.1 M and the flux was maintained in $0.5\,ml\,min^{-1}$. Pullulan from Shodex Denko was used as reference.

2.3. Modification of GA by addition of glycidyl methacrylate

The GA was purified by precipitation from an aqueous solution by addition of ethanol. GA-MA was synthesized and purified according to the method proposed by Reis et al. (2001). Briefly, the GA was dissolved in DMSO. Then, DMAP and GMA were added. The solution was stirred during 48 h at room temperature. The modified polymer, quoted as GA-MA, was purified by precipitation in ethanol. The presence of glycidol on the liquid phase was investigated by GC-MS. The precipitate was dissolved in 10 ml of distilled–deionized water. The pH was adjusted to 7.0 (using HCl) and dialyzed during 5 days at 4 °C using a dialysis tubing (Sigma, D-0530, lot 103H0525). After, the material was lyophilized to obtain the GA-MA.

2.4. Synthesis of hydrogels

To synthesize hydrogels, 1.5 g of GA-MA was dissolved in water and deoxygenated by bubbling N_2 during 15 min at room temperature. The cross-linking process was trigged by addition of desired volumes of SP 1.0 M and of TEMED 0.3 M aqueous solutions. In each synthesis the total volume was 10.0 ml. The concentrations of SP and TEMED in feed solution, used to cross-link the hydrogels, are shown in Tables 1

Table 1
Values of equilibrium swelling ratio (q) at temperatures from 25 to 45 °C, pH 7.0 and 1.0 for two different hydrogels

pH	25.0 °C	30.0 °C	37.0 °C	45.0 °C
Hydrogels cross-linked with 70 mM of SP and 9 mM of TEMED on the feed solution				
1.0	6.13 ± 0.07	6.34 ± 0.08	6.67 ± 0.08	Hydrolysed
7.0	7.45 ± 0.01	7.48 ± 0.01	7.49 ± 0.01	7.54 ± 0.02
Hydrogels cross-linked with 20 mM of SP and 6 mM of TEMED on the feed solution				
1.0	4.63 ± 0.06	5.48 ± 0.05	5.73 ± 0.11	Hydrolysed
7.0	6.90 ± 0.14	6.91 ± 0.02	6.95 ± 0.01	6.96 ± 0.01

and 2. As soon as possible, the system was transferred to a cylindrical mould (a syring with double embolus). Finally, the formation of hydrogel was observed by complete gelation. The hydrogels were immersed in distilled–deionized water during 1 week to remove unreacted chemicals (TEMED and SP) and low molecular weight polysaccharide chains not incorporated to the network. The water was renewed every 24 h.

2.5. Swelling experiments

The equilibrium water content (EWC) in cylindrical hydrogels were determined, through gravimetric measurements, using the equation:

$$\mathrm{EWC} = \frac{W_s - W_d}{W_s} \times 100\% \quad (1)$$

where W_d and W_s are, respectively, the mass of dried and swollen hydrogel. It was considered that the equilibrium was achieved if the mass of sample did not change more than 0.01 g during 24 h, at pH 7.0. Hydrogels in equilibrium swelling were obtained in pH 7.0 (distilled and deionized water) and pH 1.0 (HCl aqueous solution) at 25, 30, 37 and 45 °C. According to Vervoort et al. (1998), Hariharan and Peppas (1996) and Ranjha and Doelker (1999), the equilibrium swelling ratio, q, was, for each case, calculated using the equation:

$$q = \frac{W_s}{W_d} \quad (2)$$

Averaged values of q and EWC for each hydrogel in those pH and temperatures were calculated from triplicates.

3. Results and discussion

3.1. Determination of molecular mass of GA by HPLC

The obtained value of $\bar{M}_n$ and $\bar{M}_w$, in kg mol^{-1}, for the purified GA is 4.87×10^2 and 2.96×10^3, respectively, resulting in a polydispersity of 6.08. As shown in Fig. 1, the distribution of molecular mass is bimodal. This means that the GA is constituted of chains having high molecular weight but the value of length spreads, as expected in polysaccharides from exudates (Paula and Rodrigues, 1995).

3.2. Characterization of GA-MA

A proposed scheme for the reaction between GA and GMA, catalyzed by DMAP in DMSO is shown in Fig. 2. According to van Dijk-Wolthuis et al. (1995, 1997), two different pathways could be considered for this reaction. The presence of glycidol and its respective degradation products was detected by the GC-MS (the chromatogram is not shown in this report). In the conditions used in this work,

Table 2
Values of EWC at temperatures from 25 to 45 °C, pH 7.0 and 1.0 for two different hydrogels

pH	25.0 °C	30.0 °C	37.0 °C	45.0 °C
Hydrogels cross-linked with 70 mM of SP and 9 mM of TEMED on the feed solution				
1.0	83.70 ± 0.19	84.22 ± 0.21	85.06 ± 0.18	Hydrolysed
7.0	86.58 ± 0.03	86.63 ± 0.01	86.65 ± 004	86.74 ± 0.04
Hydrogels cross-linked with 20 mM of SP and 6 mM of TEMED on the feed solution				
1.0	78.41 ± 0.31	81.77 ± 0.19	82.53 ± 0.35	Hydrolysed
7.0	85.51 ± 0.29	85.54 ± 0.03	85.62 ± 0.01	85.65 ± 0.01

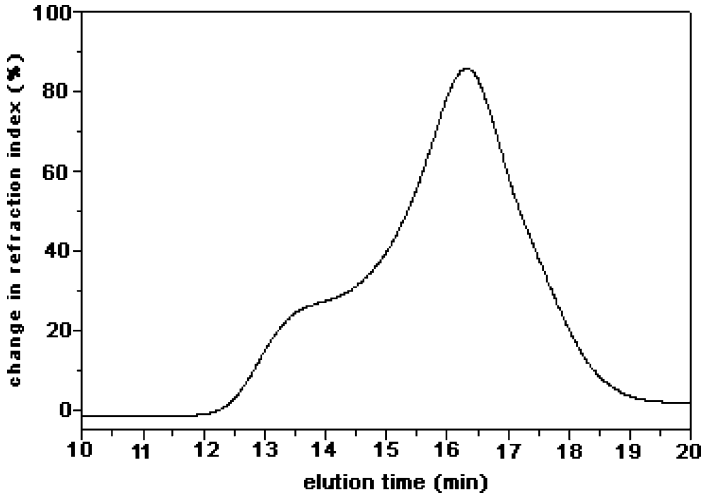


Fig. 1. Chromatogram of galactomannan (GA) obtained from HPLC analysis.

after 16.65 min the peaks related to *m/z* 73 (1%, $[M - H]^+$), *m/z* 56 (2.6%, $[M - H_2O]^{\bullet+}$), *m/z* 45 (10.6%, $[M - CHO]^{\bullet+}$), base-peak in *m/z* 44 (100%, $[M - CH_2O]^{\bullet+}$), 43 (82.9%, $[M - CH_3O]^{\bullet+}$), *m/z* 42 (9.3%, $[M - (CH_2O) - H_2]^{\bullet+}$) was observed in the CG-MS chromatogram. Then, the presence of glycidol as by-product suggests that the reaction of GA with GMA occurs by a transesterification pathway. This was earlier observed by van Dijk-Wolthuis et al. (1997) and Vervoort et al. (1997) in methacryllated-dextran and methacrylated-inulin hydrogels, respectively.

3.3. Characterization of hydrogels through FT-IR analysis

The scheme representing the proposed reaction for hydrogel formation is shown in Fig. 3. An alteration on the band at 1636 cm^{-1}, in FT-IR spectrum of hydrogel when compared to the GA-MA spectrum, may be observed in Figs. 4, 5A, B and 6A, B. The major difference was attributed to vibration of C=C groups on GA-MA, since that after the gel formation it was not detectable anymore. Another interesting change in the hydrogel FT-IR spectrum, in relation to

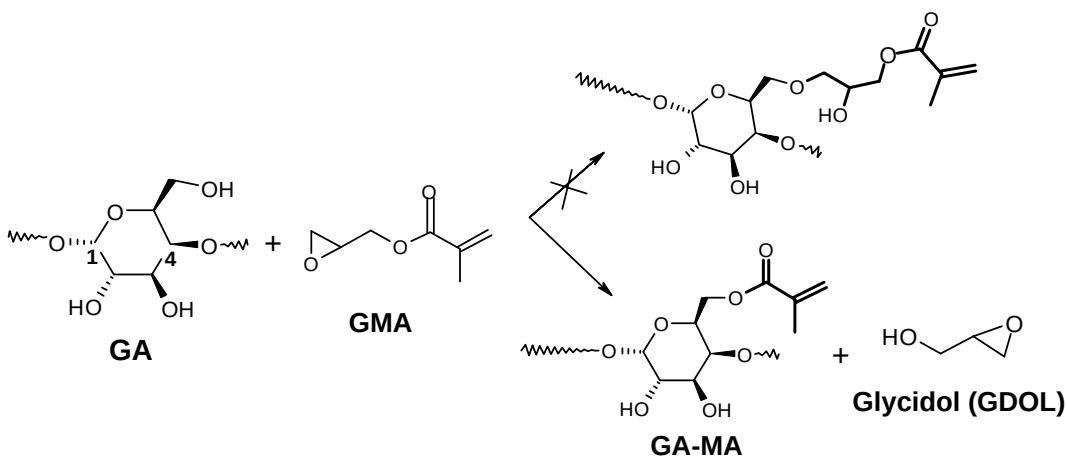


Fig. 2. Schematic representation for the reaction between GA and GMA.

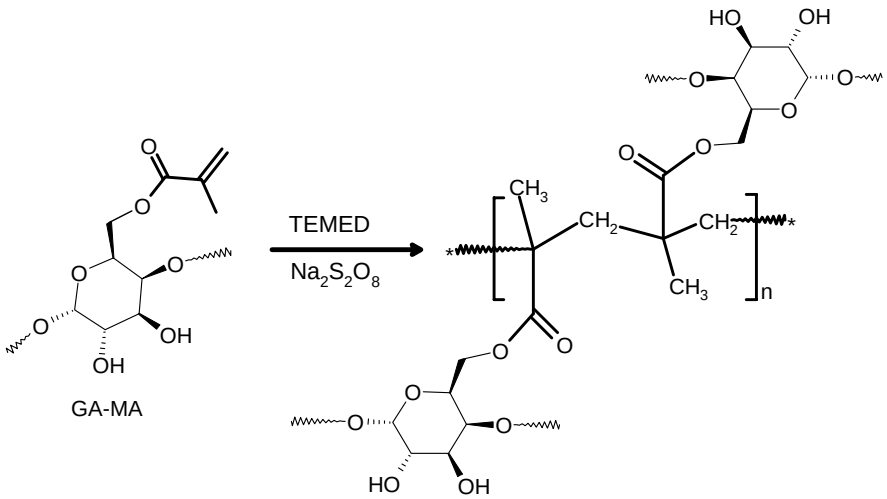


Fig. 3. Schematic representation for the reaction of hydrogels formation.

the GA-MA FT-IR spectrum may be seen in Fig. 6A and B. The band present in 1717 cm^{-1}, attributed to axial deformation of C=O of conjugated ester groups of GA-MA, shifts to 1730 cm^{-1}. This was explained as due to the loss of conjugation from ester groups after the cross-linking process (Ferreira et al., 2000).

The FT-IR spectra of GA, GA-MA and hydrogel are shown in Fig. 4. A broad band, attributed to hydroxyl groups present in these materials, may be observed

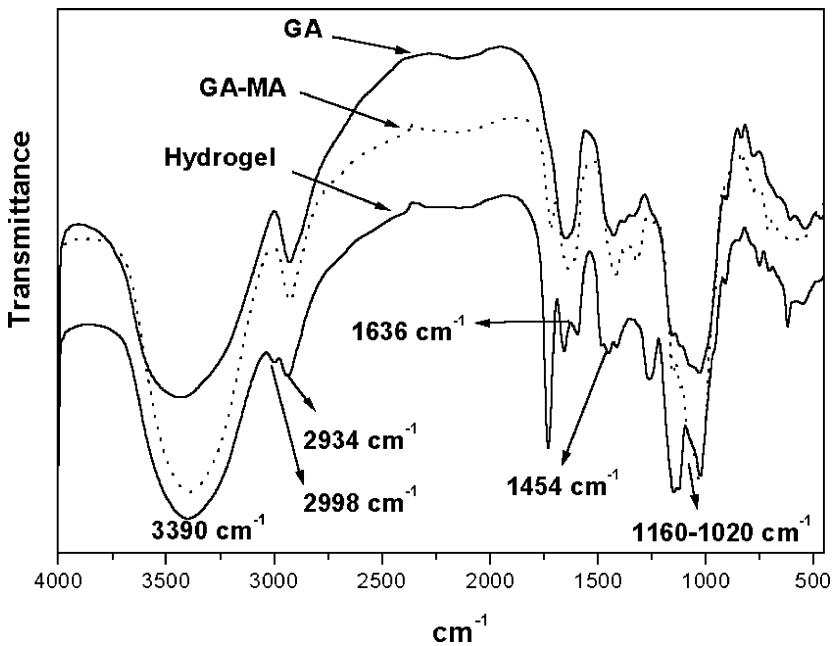
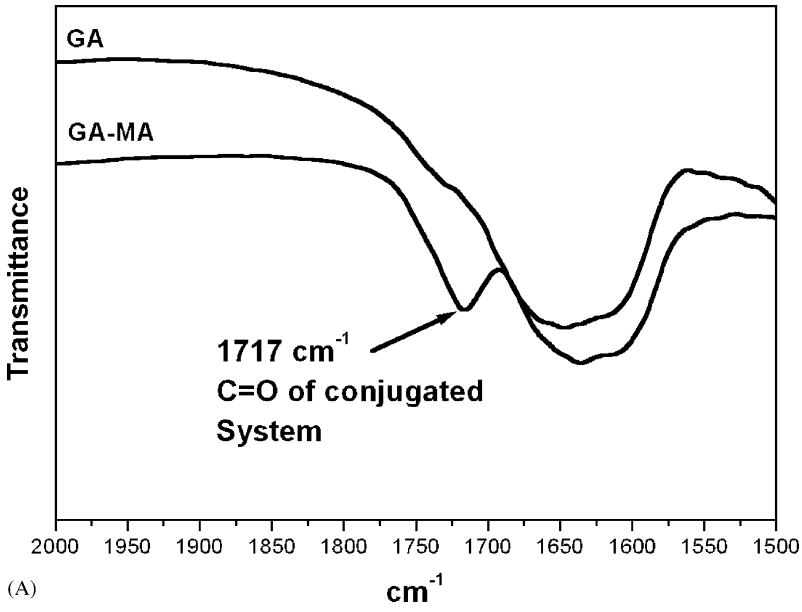
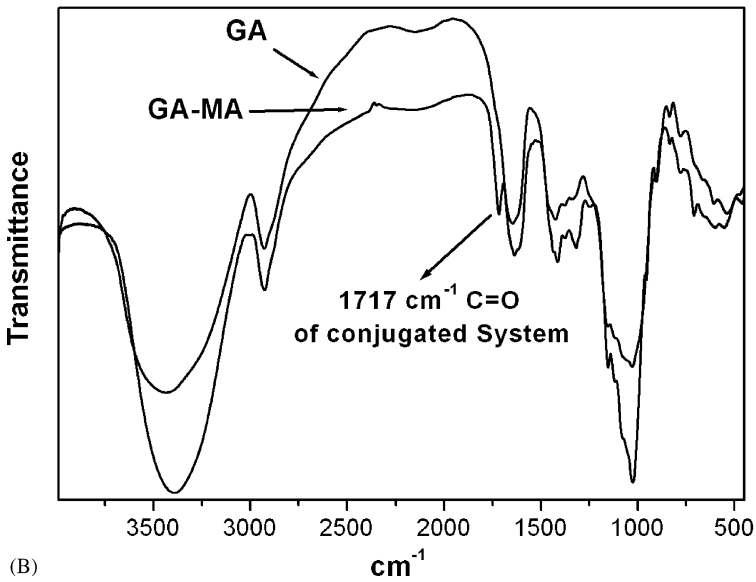


Fig. 4. FT-IR spectrum of GA, GA-MA and hydrogel.



(A)



(B)

Fig. 5. (A) FT-IR spectrum of GA and GA-MA from 2000 to 1500 cm^{-1}. (B) FT-IR spectrum of GA and GA-MA from 4000 to 450 cm^{-1}.

at 3390 cm^{-1}. Bands at 2934 and 1454 cm^{-1} were assigned to $–CH_2–$ and $–CH_3$ groups. The band at 1160–1020 cm^{-1}, assignable to C–O and/or C–O–C groups from alcohol and ethers is present in all three spectra. The chemical modification of GA by addition of GMA may be observed in the FT-IR spectrum of GA-MA compared to the spectrum of GA (Fig. 5A). The spectrum of GA-MA is characterized by the appearance of a band at 1717 cm^{-1}, attributed to the carbonyl groups in a conjugated system. In addition, the presence of C=C groups in GA-MA was indirectly detected by the appearance of a slight band

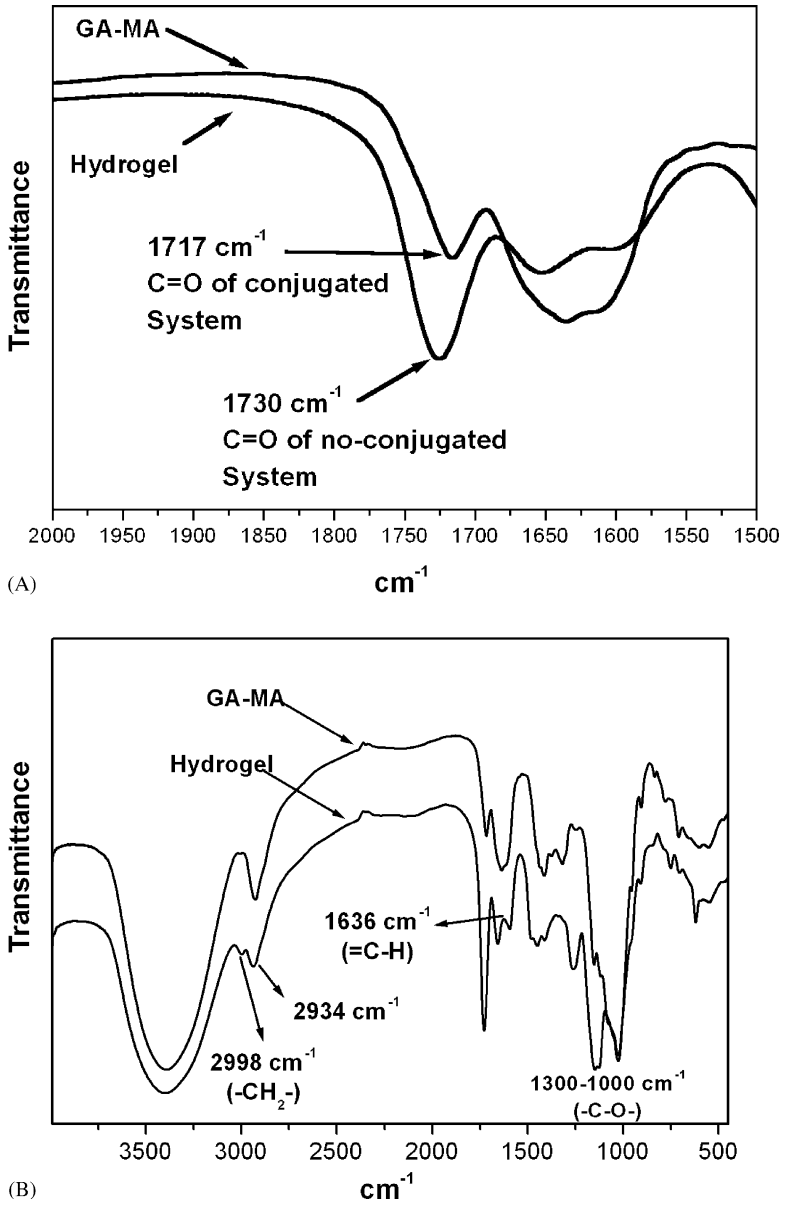


Fig. 6. (A) FT-IR spectrum of GA-MA and hydrogel from 2000 to 1500 cm^{-1}. (B) FT-IR spectrum of GA-MA and hydrogel from 4000 to 450 cm^{-1}.

at 2998 cm^{-1} and also due to the decrease of intensity of band at 1636 cm^{-1} (Figs. 4 and 6B). It should be noted that this was not observed in the FT-IR spectra of GA or GA-MA, shown in Fig. 5B. On the other hand, after the cross-linking process the intensity of the band at 2998 cm^{-1}, related to the $–CH_2–$ and C–H groups, increases and simultaneously the intensity of band at 1636 cm^{-1}, related to vibration of C–H bond on =C–H groups, decreases as shown in Fig. 6B.

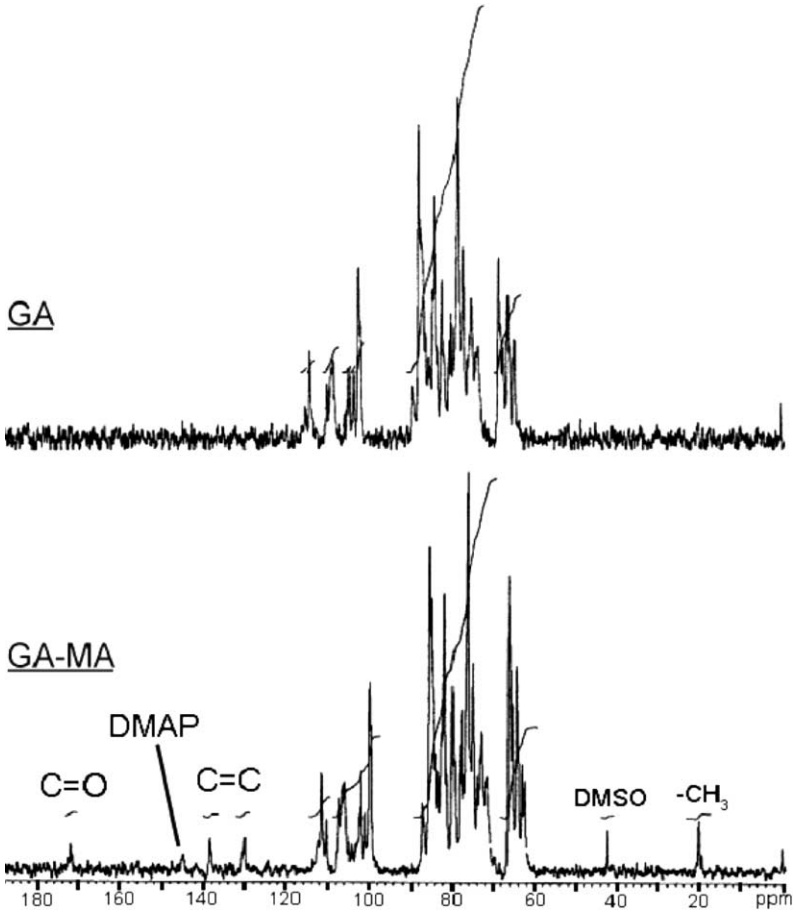


Fig. 7. ^{13}C NMR spectrum of GA and GA-MA recorded in D_2O (methyl carbon: δ 20.19 ppm; vinyl carbon: δ 138.52 and 130.0 6 ppm; carbon carbonyl: δ 171.87 ppm of GMA).

3.4. Characterization of GA, GA-MA and hydrogels through NMR analysis

By comparison of ^{13}C NMR spectrum of GA and GA-MA, shown in Fig. 7, it was possible to detect the presence of the signal attributed to the vinyl carbon of methacrylate group (δ 138.52, 130.06 ppm), to the carbonyl (δ 171.87 ppm) and to the methyl (δ 20.19 ppm) on GA-MA. The signal at δ 42.17 and 144.78 ppm was attributed to traces of DMSO and aromatic carbons of DMAP. It could be pointed out that 5 days of dialysis were not enough to completely remove the DMSO and DMAP from the GA-MA.

From ^1H NMR spectra of GA, GMA and GA-MA, shown in Fig. 8, the presence of signals at δ 6.21 and 5.78 ppm attributed to the vinyl protons and at δ 1.97 ppm attributed to the methyl protons were observed. The appearance of these signals confirms the presence of methacryloil groups on GA-MA.

3.5. Characterization of hydrogels through swelling measurements

Swelling ratios, q, were obtained using dried hydrogels in cylindrical form. Values of q for the hydrogels as the temperature was changed from 25 to 45 °C in pH 7.0 and 1.0 are shown in Table 1. It may be observed that in pH 1.0 the hydrogels are less swollen than in pH 7.0. But, in pH 1.0 the q slightly increases as the temperature is raised. It could be due to hydrolytic

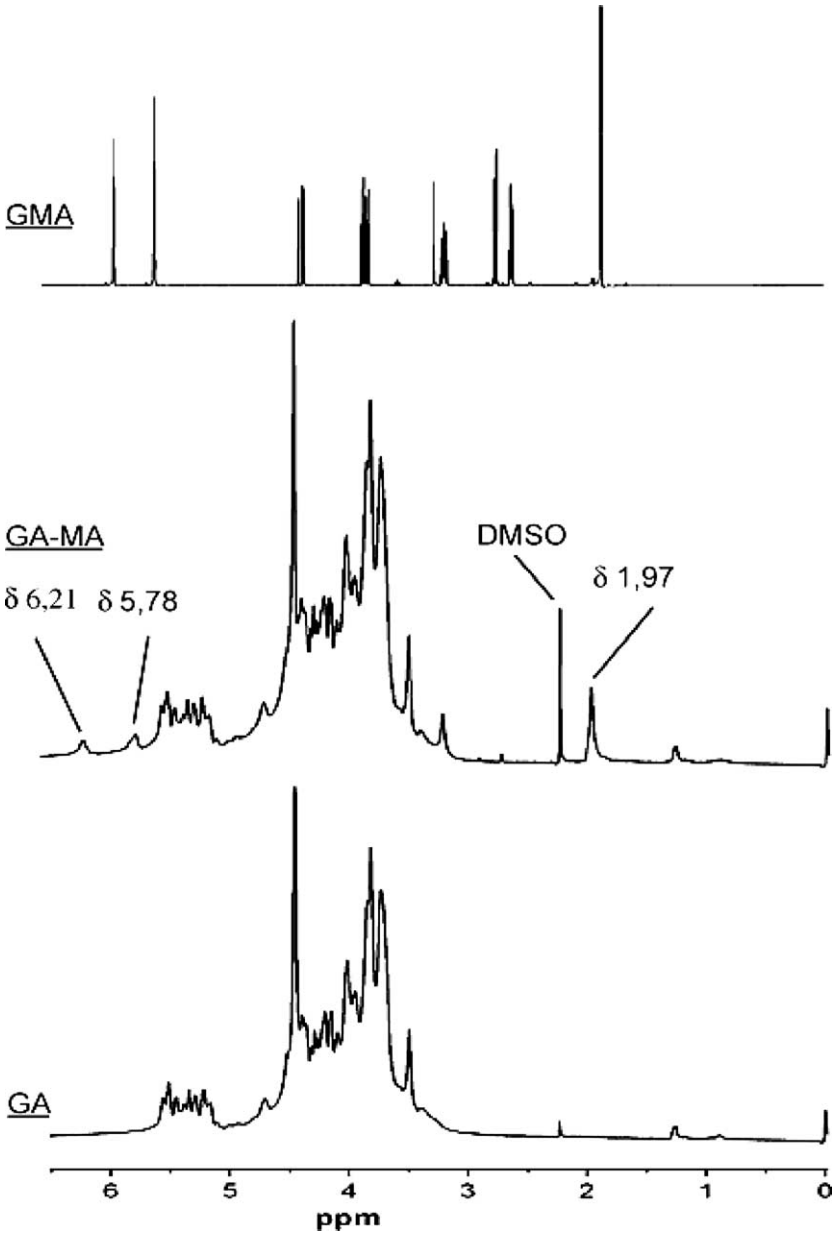


Fig. 8. ^{1}H NMR spectrum of GMA, recorded in CD_3Cl. Spectra of GA and GA-MA were recorded in D_2O (methyl protons: δ 1.97 ppm; vinyl protons: δ 6.21 and 5.78 ppm of GMA).

capability of such hydrogels in acidic conditions because it was verified that in pH 1.0 and at 45 °C the ester linkages are hydrolyzed and the gel phase completely disappears. But the hydrolysis does not occur at 37 °C up to 48 h immersed at that temperature even in pH 1.0 (see Figs. 11 and 12). Thus, it could be pointed out that the threshold temperature for such hydrolysis in pH 1.0 is higher than 37 °C. The values of EWC in temperatures from 25 to 45 °C, in pH 7.0 and pH 1.0 for the two different hydrogels are shown in Table 2.

From the data of Table 1, it may be observed that the amount of SP and TEMED used on hydrogel synthesis is significant to the hydrogels swelling properties. When the concentration of feed solution is 70 mM in SP and 9 mM in TEMED the q and EWC values are higher than when such concentrations are 20 mM in SP and 6 mM in TEMED. This fact was explained as related to the rate of cross-linking reaction. Higher concentrations of SP and TEMED result in formation of a more elastic network yielding hydrogels with less restraining forces to swell and, thus, higher values of q and EWC could be achieved. Such behavior was earlier observed by Vervoort et al. (1998) in methacrylated-inulin hydrogels. After dried the re-hydrated gel does not recover the previous water content. For example, in the first immersing the just-synthesized hydrogels presented q values close to 12–13. By immersing previous dried cylindrical hydrogels, the values of equilibrium swelling ratio decreases (Table 1).

3.6. Determination of M_C and υ_e of hydrogels

When in contact with appropriate solvent, the dehydrated hydrogels swell and cause elongation and/or stretching of the polymer network. The entrance of fluid is against-balanced by a retractive force from the elasticity of polymer chains (Peppas et al., 2000). This retractive force is inversely proportional to the averaged molecular weight of the polymeric chain segment between adjacent cross-links, M_C. If M_C is high, the polymer chain would be more elastic and would swell quickly when in contact with appropriate liquid (Kulkarni et al., 1999). As the cross-linking degree, υ_e, is inversely proportional to q, the values of υ_e may be calculated from the values of M_C.

In order to calculate the values of M_C for the hydrogels synthesized in this work, the Eq. (3), due to Flory (1953), was used. The density of polymer, δ_p, is 1.1847 g ml^{-1} and was determinate from gravimetric measurements at 25 °C. The molar volume of solvent, $\bar{V}_s$, was collected from the literature (Lide, 1996).

$$M_C = -\delta_p \bar{V}_s \phi^{1/3} [\ln(1-\phi) + \phi + \chi\phi^2]^{-1} \quad (3)$$

The volume fraction of polymer in the equilibrium swollen state, ϕ, was calculated using Eq. (4). The density of solvent, δ_s, was also collected from literature (Lide, 1996). The weight of dried cylindrical hydrogel, W_d, and the weight of the hydrogel after had achieved the equilibrium swelling, W_s, were determined.

$$\phi = \left[1 + \frac{\delta_p}{\delta_s}\left(\frac{W_d}{W_s}\right) - \frac{\delta_p}{\delta_s}\right]^{-1} \quad (4)$$

The polymer–solvent interaction parameter, χ, was calculated using the Eq. (5), proposed by Flory (1953). This equation has been widely used, for instance by Aithal and Aminabhavi (1990a), Aithal et al. (1990b) and Kulkarni et al. (1999).

$$\chi = [\phi(1-\phi)^{-1} + N\ln(1-\phi) + N\phi] \times \left[2\phi - \phi^2 N - \phi^2 T^{-1}\left(\frac{d\phi}{dT}\right)^{-1}\right]^{-1} \quad (5)$$

The dependence of polymer volume fraction to the temperature, $d\phi/dT$, was obtained from q measured at 25, 30, 37 and 45 °C. For each swollen hydrogel the value of N, a intrinsic parameter, was determined for each temperature and pH using the equation:

$$N = \left(\left(\frac{\phi^{2/3}}{3}\right) - \left(\frac{2}{3}\right)\right)\left(\phi^{1/3} - \left(\frac{2\phi}{3}\right)\right)^{-1} \quad (6)$$

The values of M_C for the hydrogels synthesized using 70 and 20 mM of SP and 9 and 6 mM of TEMED on feed solution at the temperatures of 25, 30, 37 and 45 °C are shown in Fig. 9.

According to Gwaily et al. (2003), the cross-link density, υ_e, defined as the number of elastically effective chains wholly included in a perfect network by unit volume, may be calculated using the Eq. (7):

$$\upsilon_e = \frac{\delta_p N_a}{M_C} \quad (7)$$

where N_a is the Avogadro's number.

The values of υ_e obtained for the two different concentrations of SP and TEMED in the feed solution at several temperatures are presented in Fig. 10. The hydrogels cross-linked using 20 mM of SP and 6 mM of TEMED on feed solution present higher values of υ_e when compared to the hydrogels cross-linked using the 70 mM of SP and 9 mM of TEMED in feed solution (Fig. 10). This indicates that the amount of SP and TEMED influences the value of υ_e. It is apparent that the temperature does not influence significantly in the values of M_C and υ_e of the hydrogels. Thus, the hydrogels from GA-MA are thermostable.

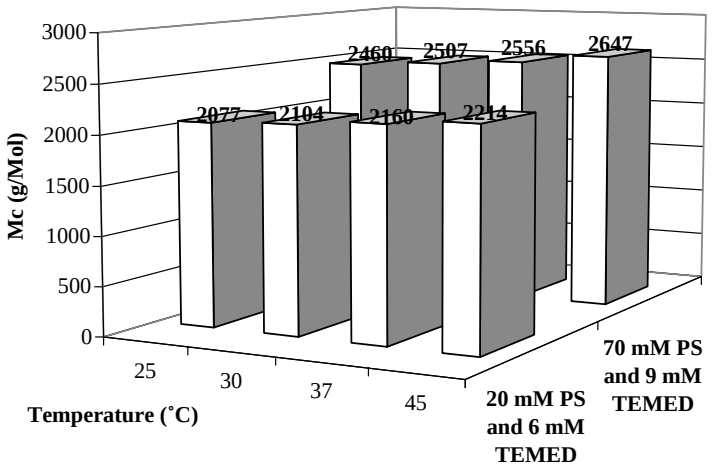


Fig. 9. Values of average molar mass between two adjacent cross-links (M_C) of different hydrogels in pH 7.0.

Fig. 11 shows the swelling ratio of hydrogels immersed in aqueous solution of pH 1.0 (HCl) at 37 °C, as a function of time. At first hour of immersion the swelling ratio is ca. 2.2 but it increases to 6.0 after 24 immersed and completely hydrolyses if immersed more than 48 h. This is an important aspect because it shows that the hydrogels are resistant to acidic environment during a period of 48 h. In case of such hydrogels to be used for delivering, once ingested its properties will not be affect, i.e. the hydrogel remains not hydrolyzed because the maximum residence time in stomach is ca. 12 h, according to Reddy et al. (1999).

Fig. 12 show the photos of hydrogels cross-linked using 20 mM of SP and 6 mM of TEMED in feed solution (A–C) and hydrogels cross-linked using the 70 mM of SP and 9 mM of TEMED in feed solution (D–F). Parts A and D refer to dry state, parts B and E to 5 h immersion in pH 1.0 at 37 °C and parts C and F refer to hydrogels immersed during 36 h in pH 1.0 at 37 °C. From the photos it is clear that hydrogels remain the cylindrical form up to 48 h of immersion in pH

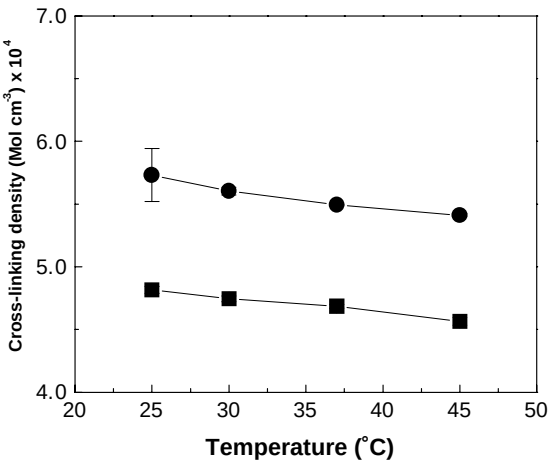


Fig. 10. Cross-linking density as a function of temperature in pH 7.0 (■) hydrogels cross-linked with 70 mM of SP and 9 mM TEMED, (●) hydrogels cross-linked 20 mM of SP and 6 mM TEMED.

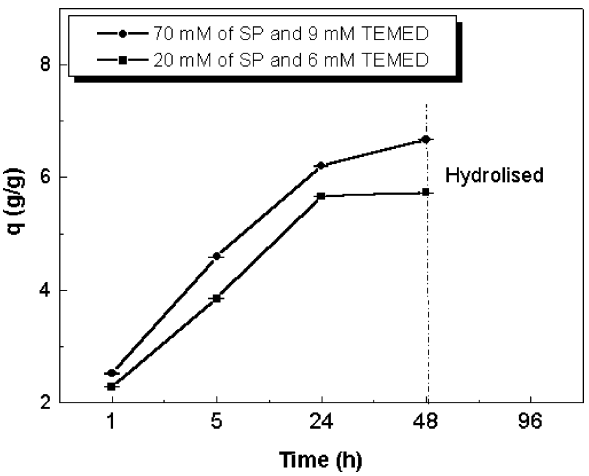


Fig. 11. Dependence of swelling ratio as a function of time, obtained on pH 1.0 at 37 °C.

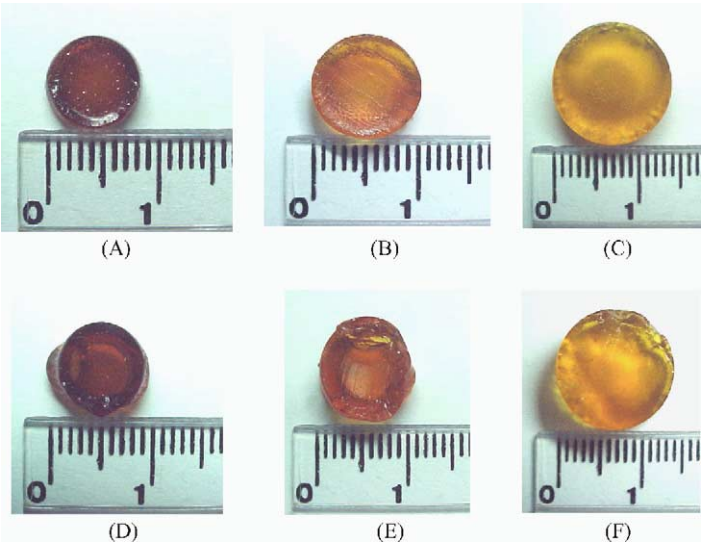


Fig. 12. Photos of hydrogel obtained from the GA-MA. Parts A and D refer to dry state, parts B and E to 5 h immersion in pH 1.0 at 37 °C and parts C and F refer to hydrogels immersed during 36 h in pH 1.0 at 37 °C. The scale is given in centimeters.

1.0. As expected, the hydrogel volume increases with the time. In Fig. 12, the scale is given in centimeters.

4. Conclusions

Methacrylated galactomannan (GA-MA) may be synthesized by reaction of GA with GMA in the presence of DMAP as catalyst. The reaction proceeds via transesterification, leading to the addition of methacryloil groups on GA chains. The GA-MA is the main product and glycidol is a by-product. Hydrogels from the GA-MA can be prepared by polymerization just by addition of SP and TEMED in a deoxygenated GA-MA aqueous solution. During the polymerization process, the cross-linking occurs on methacryloyl groups, resulting in a three-dimensional hydrogels network. The swelling properties of hydrogels depend slightly on the amount of TEMED and SP in feed solution. The pH does not affect significantly the equilibrium swelling ratio of the hydrogels. In pH 1.0, the swelling ratio increases as the temperature is raised from 25 to 37 °C. At this temperature, the hydrogels remain their form during 48 h. At 45 °C and pH 1.0 the hydrogels completely hydrolyses after 24 h. At pH 7.0 no hydrolysis was observed even after the hydrogel is immersed during 10 days. The EWC on hidrogel is around 84–86 wt.%. This relatively high water content in the hydrogel suggests that water-soluble drugs may be loaded into the hydrogel matrix for use in controlled-release dosage forms.

These results suggest that hydrogels based on glycidyl methacrylated derivative from galactomannan, GA-MA, may be used in pharmaceutical applications as an alternative for controlled released systems.

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