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ORIGINAL PAPER

Characterization of polysaccharide hydrogels for modified drug delivery

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Abstract Hydrogels are hydrophilic macromolecular networks that are capable of retaining a large amount of water. A precise description of these systems is actually quite complex and the practical use of hydrogels for drug delivery and biomedical applications is often not supported by a well-defined knowledge of the overall structure of the polymeric network. In this paper, we report the characterization of two different systems: a chemical network based on Guar Gum (GG) and a physical gel prepared with Xanthan (Xanth) and Locust Bean Gum (LBG). The dynamo-mechanical properties of the gels were analysed: the cohesiveness and the adhesion of the networks were strongly dependent on time, temperature, and composition. The kinetics of the chemical crosslinking was followed by means of rheological measurements, i.e. recording the mechanical spectra of the gelling system, and the power law exponent at the gel point was evaluated. Furthermore, the networks, loaded with model drugs with different steric hindrance, were used as matrices for tablets and the rate of release of such model drugs was studied. The diffusion of the guest molecules was deeply dependent on their dimensions; in the case of Xanth–LBG tablets the release profiles were almost independent from the different cohesion properties of the starting hydrogel composition.

Keywords Guar Gum · Locust Bean Gum · Xanthan · Hydrogels · Drug delivery · Gel point

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Introduction

In the field of drug delivery, much effort has been devoted, in the last decades, to the study of appropriate systems with special properties, in order to avoid or minimize the side-effects and to improve the efficacy of the therapy. In this sense, polymers appear to be very attractive for their peculiar physico-chemical characteristics (Hoffman 2002).

In this paper, two different types of polysaccharidic networks are considered: the chemical one and the physical one. The first one, obtained with Guar Gum (GG) and Glutaraldehyde (Ga), has been already tested for colon drug delivery (Gliko-Kabir et al. 1998) and here a mechanical characterization is reported as a function of temperature. Furthermore, the gel point was detected and the critical exponent was evaluated. For the second type of gel, the Locust Bean Gum (LBG) and Xanthan (Xanth) polymers have been tested and their potential use for modified drug delivery was investigated; in fact, it is known that Xanth forms elastic and thermoreversible gels when mixed with LBG (Mao and Rwei 2006). Numerous models, often even contradictory, have been proposed for this network (Lundin and Hermansson 1995 and the refs. therein; Bresolin et al. 1997, 1999; Ojinnaka et al. 1998; Liu et al. 1998; Wang et al. 2002) and the gel formation mechanism is still controversial. According to one of the most recent research (Richter et al. 2005), the Xanth molecules interact with LBG mainly via the backbones of both polysaccharides. Entanglements are initially formed between the Xanth and LBG chains and then, when the supramolecular structure extends to the overall macroscopic sample, the gel point takes place. We confirmed that the synergistic strength (Copetti et al. 1997) of the interactions depends on the mixing temperature: below the helix-coil transition temperature of Xanth, weak elastic

gels are formed, while strong elastic gels are obtained on heating the mixtures. Furthermore, the hardness and the elastic modulus presented a maximum value when the two polymers were mixed in the same weight ratio. The different networks have been tested as matrices for drug release of model drugs (theophylline, TPH and myoglobin, MGB).

Experimental

Materials and methods

Guar Gum was the gift of Lamberti s.p.a. (Italy); LBG was provided by Carbomer (USA), while Xanthan Gum from *Xanthomonas campestris* (Xanth) was provided by Fluka (Italy). All other products and reagents were of analytical grade.

All polysaccharides were used after purification: a given amount of Xanth (polymer concentration, cp = 0.5% w/v) was dissolved in distilled water, under magnetic and mechanical stirring, at room temperature for 48 h, while GG and LBG (cp = 0.5% w/v) were dispersed in distilled water, under magnetic and mechanical stirring, at 60 and at 80°C, respectively, for 24 h and at room temperature for 24 additional hours (Kok et al. 1999). The obtained solutions were exhaustively dialysed at 4°C against distilled water with dialysis membranes with a cut-off 12,000–14,000, and they were then freeze-dried.

The lyophilized products were stored in a desiccator until use.

GG/Ga hydrogels

For the mechanical characterization of GG/Ga (Ga at 50% (w/v), Carlo Erba, Italy), the gels were obtained according to a procedure already described (Coviello et al. 2006). In a beaker, to the purified and acidified polymer solution (cp = 1.5% w/v), the calculated amount of Ga, needed to obtain a remarkable excess with respect to the stoichiometric ratio, was added. In our case, the ratio between the crosslinker moles and the moles of polymer repeating units (r) was set equal to 4. The reaction mixtures were magnetically stirred for 30 min and then kept in a thermostatted bath at 37°C. At fixed time intervals, the samples were then analysed with the Texture Analyzer (see below) (Fig. 1).

For the release experiments from tablets, the reaction mixtures were magnetically stirred for 30 min and then kept in a thermostatted bath at 30°C for 48 additional hours for gel setting. The obtained self-sustaining gels, which settled in a 10-ml beaker, showed the geometry of a cylinder with a diameter of 22 mm and a height of 18 mm.

The hydrogels of GG/Ga were previously dialysed at 4°C against distilled water, using dialysis membranes with a cut-off 12,000–14,000, to remove the unreacted Ga, which was spectrophotometrically determined in the dialysate at the appropriate wavelength (polymeric form λ = 235 nm; monomeric form λ = 280 nm), using quartz cells with pathlengths of 1 cm. In fact, as described in the literature, Ga exists in solution in various forms (free aldehyde, mono- and dehydrated Ga, monomeric and polymeric cyclic hemiacetals, and α,β-unsaturated polymeric forms) (Korn et al. 1972; Whipple and Buta 1974; Kawara et al. 1992) and, therefore, it is not possible to give an exact description of the resulting network.

After dialysis and freeze-drying, the hydrogels were loaded with the model drugs, TPH (Carlo Erba, Italy) and MGB (Fluka, Germany), using different loading procedures: in the case of TPH, the GG/Ga samples were soaked in a saturated solution of the drug for 48 h and then washed with distilled water to remove the excess of the imbibing solution. In the case of MGB, drug loading was carried out by directly inserting with a needle a given amount of an aqueous MGB saturated solution into the matrices until they were completely and homogeneously imbibed, as evidenced by the uniform brown colour acquired by the matrix.

LBG/Xanth hydrogels

The LBG/Xanth hydrogels, for the release experiments from tablets, were prepared by mixing appropriate amounts of galactomannan and Xanth solutions at 75°C for 15 min, previously autoclaved at 121°C for 20 min. The obtained gels were loaded with MGB, dissolving a given amount of the model drug in the LBG solution before the addition of the Xanth solution (Fig. 2).

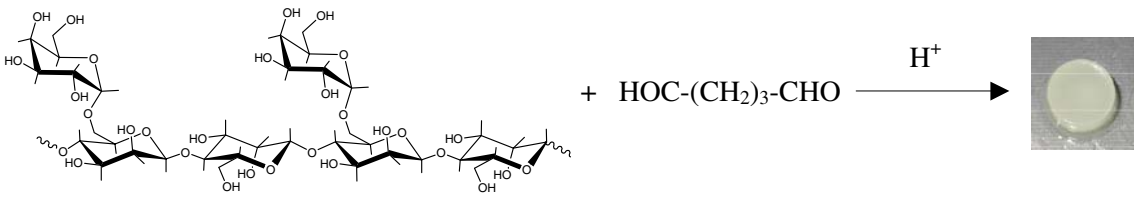


Fig. 1 Repeating unit of GG, chemical structure of Ga, and a photograph of the obtained chemical gel

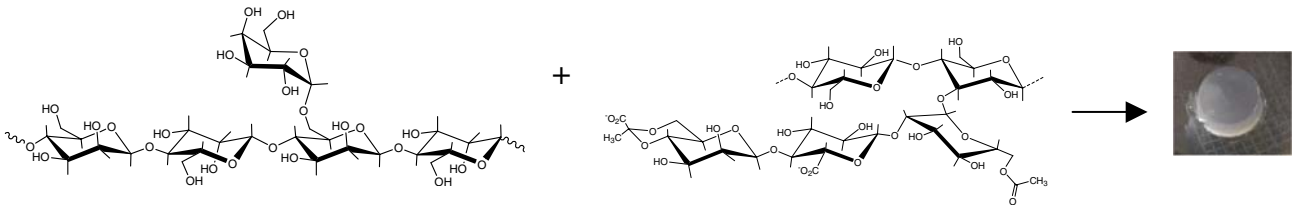


Fig. 2 Repeating unit of LBG, Xanth, and a photograph of the obtained physical gel

Tablets preparation

The tablets of GG/Ga and LBG/Xanth were prepared from the freeze-dried samples obtained with the hydrogels using an IR die (Perkin-Elmer hydraulic press) with a force of 5.0 kN for 30 s.

All tablets had a weight of 190 ± 10 mg, a diameter of 13.00 ± 0.05 mm, and a thickness of 1.50 ± 0.10 mm.

Reference tablets were prepared by freeze-drying aqueous solutions containing the single polymers and the model drug, followed by compression at the same conditions reported above.

Dissolution test

Release experiments from the model dosage forms were carried out in distilled water (500 ml, pH = 5.4), according to Ph. Eur. 5th, using the rotating basket apparatus at 37.0 ± 0.1°C and 100 rpm. Aliquots of dissolution medium (4 ml) were taken at fixed time intervals and the amount of released TPH or MGB was spectrophotometrically determined at 272 and 409 nm, respectively, using quartz cells with pathlength of 1 cm. The release experiments were carried out in triplicate.

The results are reported as the relative percentage release, $(M_t/M_\infty) \times 100$, where M_t indicates the amount of drug released at time t and M_∞ indicates the release of the total amount of the drug loaded in the formulation.

Rheological characterization

The rheological characterization of the GG/Ga and LBG/Xanth gels was performed by means of a controlled stress rheometer (Haake Rheo-Stress RS300; Thermo Haake DC50 water bath); a grained plate-plate device (Haake PP35 TI: diameter = 35 mm; gap between plates = 1 mm) was used in order to reduce the extent of the wall slippage phenomena (Lapasin and Pricl 1995). Rheological properties were studied in oscillatory experiments; mechanical spectra were recorded in the frequency range 0.001–10 Hz. The linear viscoelastic region was assessed, at 1 Hz, by stress sweep experiments; constant deformations $\gamma = 0.1$ and $\gamma = 0.01$ for GG/Ga and LBG/Xanth hydrogels, respectively, were used.

The GG/Ga hydrogels were tested immediately after the addition of Ga at 37 ± 1°C, while LBG/Xanth samples were analysed, at 25 ± 1°C, 6 days after the preparation.

The mechanical spectra of the GG/Ga system for the gel point detection were recorded, on the same sample, in a stepwise sequence during the reaction progress; a deformation of $\gamma = 0.01$ was applied in order to influence as minimum as possible the gel forming process.

Texture analysis

A software-controlled dynamometer, TA-XT2*i* Texture Analyzer (Stable Micro Systems, UK), with a 5 kg load cell, a force measurement accuracy of 0.0025%, and a distance resolution of 0.0025 mm (according to the instrument specifications) was used for the mechanical characterization of the gel samples (Tamburic and Craig 1997; Alves et al. 2000).

The hydrogel resistance to penetration and withdrawal of the probe was measured at room temperature. The pre-test speed was set up at 2.0 mm/s, the test speed at 1.0 mm/s, and the penetration depth was variable, being imposed a fixed deformation, ranging in the linear interval response of 20% for GG/Ga samples and 8% for LBG/Xanth gels, 20 and 25% for Xanth and LBG, with an acquisition rate of 200 pps.

An ebonite cylinder probe (P-10, diameter of 10 mm) was used.

After their preparation, the gels of GG/Ga were kept at 37 ± 1°C and analysed every 7 days until they degraded, while LBG/Xanth samples were kept at room temperature for 6 days before the measurements. All the systems were tested in triplicate.

Results and discussion

Mechanical characterization of GG/Ga hydrogels

Texture analysis, initially employed in the mechanical characterization of food materials, lately has emerged as a

useful technique in the field of pharmaceutical gels studies (Jones et al. 1996; Tamburic et al. 1996). From a penetration experiment, a set of parameters can be acquired: the system hardness, F_{max} (the maximum positive force required to attain a given deformation), the cohesiveness (given by the positive area under the force-distance curve until the maximum value), the adhesiveness (the negative area under the force-distance curve), and the Young modulus E (obtained from the initial slope of the stress-strain curve).

The profiles obtained for the GG/Ga gels at different storage times are shown in Fig. 3a and the corresponding calculated parameters are listed in Table 1. As it can be observed, at 37°C, the network reaches the maximum stability after 21 days. After that time, the system looses cohesiveness due to degradation reactions that, at the chosen temperature, plays an important role. As shown in Fig. 3b, the hardness steadily increases in the first few weeks until the highest values are evidenced (3 weeks) and then the degradation process prevails with a corresponding decrease in cohesion. Obviously, also the Young modulus follows a similar trend in the deformation interval that was explored.

The gelation process of GG with Ga was monitored following the behaviour of the shear storage and loss moduli over a wide range of frequencies (Fig. 4). The network structure is formed with the polymeric chains interconnected by covalent bonds with the crosslinker molecules. The gel point is reached when the largest molecular or supramolecular cluster diverges to infinity and, though it cannot be directly measured, rheological properties are very sensitive indicators. Winter and Chambon were the first ones who reported a power-law behaviour for the shear modulus over a wide range of shear frequencies of a permanently gelling system (Chambon and Winter 1985), and they generalized a scaling law of $G'(\omega) \propto G''(\omega) \propto \omega^n$ with $0 < n < 1$.

The experiments were carried out at 37°C on samples of GG immediately after the addition of Ga. In the beginning, the mixture behaved classically as a concentrated polymer solution, while, after ca. 1 h, a power-law for the frequency dependent storage and loss shear moduli was observed (Fig. 4):

$$G'(\omega) \propto \omega^{0.48},\ G''(\omega) \propto \omega^{0.43}.$$

Such power law is present over three decades in the frequency window of ω = 0.01–10 rad/s. Because of the occurrence of the crosslinkling reaction during the measurement, in our case, the two exponents cannot show the same value and, therefore, the given n value has to be taken as an estimation in the vicinity of the gel point. The percolation theory predicts n = 0.73 (Adam and Lairez 1996; de Gennes 1979; Alexander et al. 1984; Stauffer et al. 1982), the Rouse model (which assumes no hydrodynamic interactions between the polymeric clusters) predicts n = 0.66 (Adam and Lairez 1996), and mean-field theory predicts n = 1 (Martin and Adolf 1991). From literature data this exponent value ranges between 0.1 and 0.9 (Martin and Adolf 1991); thus, it appears that there is no universal value for n that, experimentally, has been found as depending upon several parameters, such as polymer concentration, molecular weight, and the specific pre-gel history (Richter et al. 2004a, b; Grisel and Muller 1998; Michon et al. 1995; Winter et al. 1994; Hsu and Jamieson 1993; Matricardi et al. 1993; Coviello and Burchard 1992). In particular, the relaxation exponent, n, decreases with increasing cross-linker concentration (Izuka et al. 1992), as it happens with our samples (n = 0.46 ± 0.03). After the gel point, the storage modulus G′ becomes larger than the loss modulus G″ and the system behaves as a visco-elastic solid with moduli parallel to each other and independent from the frequency.

Release studies from the GG/Ga matrix

The freeze-dried gels were used, after compression, to obtain tablets and to study, in distilled water at 37°C, the

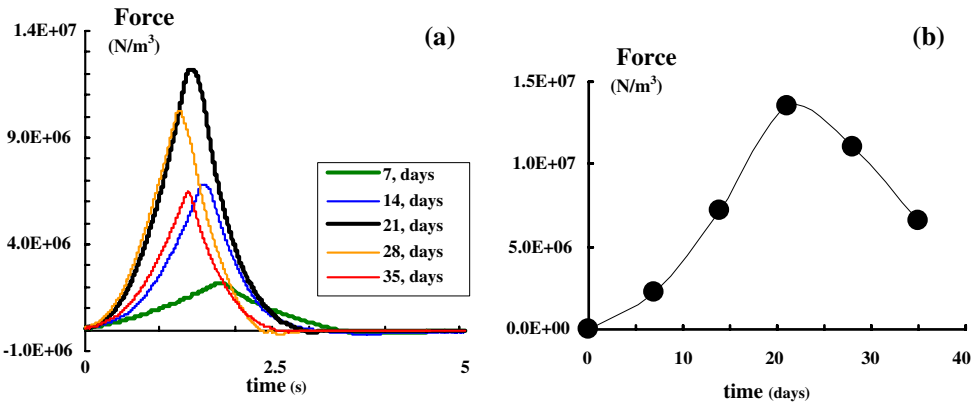


Fig. 3 Penetration profiles (per unit volume) obtained on hydrogel samples of GG/Ga kept at 37°C for different periods of time (**a**); hardness (per unit volume) of the GG/Ga hydrogel samples reported as a function of ageing time (**b**)

Table 1 Mechanical parameters obtained with the GG/Ga hydrogel kept at 37°C for different periods of time

Time (days)	Hardness[a] ($\times 10^{-6}$ N/m^3)	Cohesiveness[a] ($\times 10^{-3}$ J/m^3)	Adhesiveness[a] (J/m^3)	Young modulus, E (Pa)
7	2.22 ± 0.90	1.67 ± 0.06	158.20 ± 26.81	3878.36 ± 188.50
14	7.19 ± 0.37	5.27 ± 1.55	106.76 ± 52.34	11031.63 ± 203.05
21	13.51 ± 1.30	5.34 ± 1.14	34.15 ± 19.88	18794.19 ± 1214.62
28	11.08 ± 1.73	5.07 ± 0.67	91.99 ± 50.07	13728.87 ± 1275.12
35	6.53 ± 0.75	3.08 ± 0.22	26.58 ± 18.74	8550.61 ± 870.89

[a] The parameters are normalized per unit volume

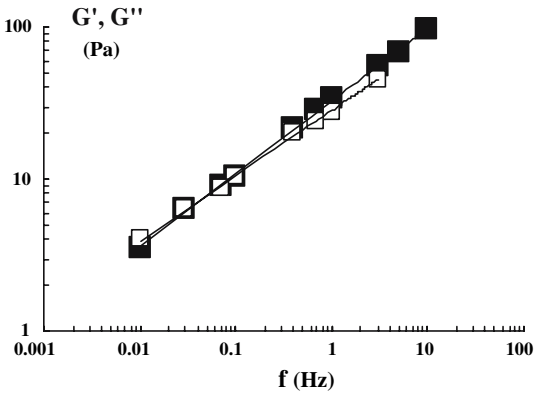


Fig. 4 Mechanical spectra of GG sample recorded, at 37°C, 56 min after the addition of Ga. G′: *dark filled square*; G″: *open square*

release profiles of the model molecules previously loaded into the network. The data obtained after 8 and 24 h are reported in Table 2. TPH, a small molecule with a radius of van der Waals of 3.7 Å, was completely released already after 8 h. MGB, a molecule with a remarkably higher steric hindrance (21.0 Å), remained practically entrapped within the matrix. On the other side, when the reference tablets (i.e. those obtained with the single polymers) were tested, a rather different behaviour was detected. For the smaller molecule, a slightly prolonged release was detected, indicating that the presence of fixed mesh size in the network facilitates, somehow, the diffusion of the guest molecule out of the matrix. When the dimensions of the model molecule increase, almost no release was detected in the 24-h time interval, indicating that the mesh sizes are much smaller than that of MGB. Thus, the hydrogel is able to discriminate between host molecules in relation to their dimensions in comparison to the mesh size of the chemical gel.

Table 2 Theophylline (TPH) and MGB release in water, at 37°C, after 8 and 24 h from tablets prepared with GG and GG/Ga

Drug	GG, $(M_t/M_\infty) \times 100$		GG/Ga, $(M_t/M_\infty) \times 100$	
	t = 8 h	t = 24 h	t = 8 h	t = 24 h
TPH	78.0 ± 3.0	100.0 ± 2.0	97.1 ± 3.1	96.8 ± 3.0
MGB	7.0 ± 0.8	41.7 ± 1.9	1.0 ± 0.4	1.0 ± 0.2

It must be pointed out that when the crosslinker was not present the observed release was still very small but significantly higher than in the presence of Ga as previously observed also when other polysaccharides were used with the same and other crosslinking agents (Coviello et al. 2006; Palleschi et al. 2006). This indicates that the entanglements of the polymeric chains act as a very efficient obstacle in particular towards the release of MGB because of its large steric hindrance. Nevertheless, being only a physical network, the entanglements lifetime is not high enough to avoid a partial liberation of the molecule. Furthermore, after 24 h, when also a partial erosion of the matrix occurs because of the dissolution of GG chains, a significant release is observed.

Mechanical characterization of LBG/Xanth hydrogels

The LBG and Xanth solutions were mixed, at a different weight ratio (Table 3), in water at 75°C; the Xanth chains were in the disordered form (T_m = 43°C). The profiles force–time (normalised per unit volume) obtained for the different investigated weight ratios by means of penetration experiments are shown in Fig. 5. The single polymers have very low cohesion and hardness, almost negligible if compared to the mixed samples. On the other side, the mixed samples show, in almost all cases, a very high hardness and also the adhesion is much higher with respect to LBG and Xanth alone. It is interesting to note that the maximum values are observed for the 1:1 mixture, followed by the 1:3 and the 3:1 compositions. Rather less cohesive appears to be the 9:1 sample and even weaker is the 1:9. A similar trend was observed when the mechanical spectra were recorded (Fig. 6). The highest storage modulus was found for the 1:1 sample, while the lowest one was detected for the 1:9 ratio; furthermore, the 1:3 mixture showed values higher than those of the 3:1 sample.

The storage and the loss moduli of the LBG/Xanth samples show the characteristic profile of the gel systems with G′>> G″ and with G′ being almost independent on the frequency in a range of several decades. On the other side, in the case of LBG and Xanth alone, the mechanical spectra are those typical of concentrated solutions (for sake

Table 3 Composition of the systems (X, c_p) LBG, Xanth, and LBG/Xanth used for the preparation of the tablets and the corresponding MGB release in water, at 37°C, after 8 and 24 h

	X[a], LBG	c^b_{ptotal}	c^b_{pLBG}	c^b_{pXanth}	$(M_t/M_\infty) \times 100$	
					t = 8 h	t = 24 h
LBG	1.00	0.50	0.50	–	4.1 ± 0.9	14.0 ± 3.0
LBG/Xanth 9:1	0.90	0.50	0.45	0.05	6.0 ± 2.4	10.1 ± 2.0
LBG/Xanth 3:1	0.75	0.50	0.33	0.13	3.2 ± 0.1	9.0 ± 0.4
LBG/Xanth 1:1	0.50	0.50	0.25	0.25	2.2 ± 0.7	6.3 ± 1.8
LBG/Xanth 1:3	0.25	0.50	0.13	0.33	2.0 ± 0.3	14.9 ± 0.5
LBG/Xanth 1:9	0.10	0.50	0.05	0.45	9.3 ± 1.5	43.8 ± 7.6
Xanth	0	0.50	–	0.50	98.5 ± 1.0	100.0 ± 1.0

[a] Weight ratio

[b] Polymer concentration, w/v

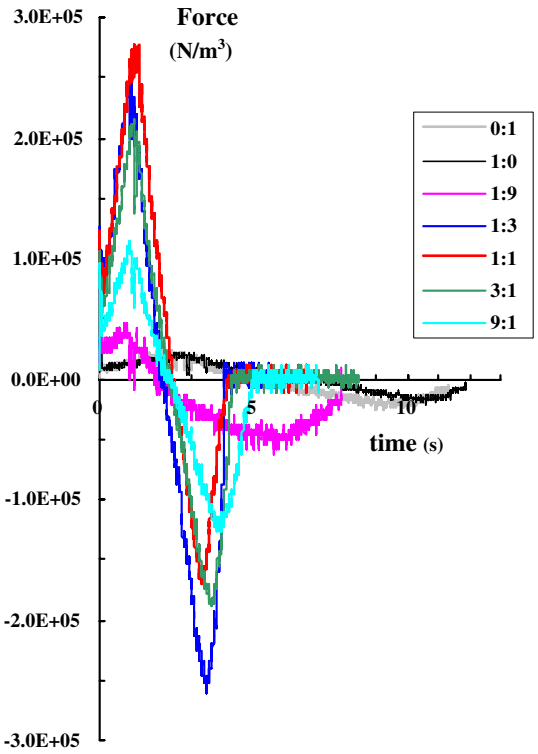


Fig. 5 Penetration profiles (per unit volume) obtained on samples of LBG, Xanth, and LBG/Xanth at different weight ratios prepared at 75°C

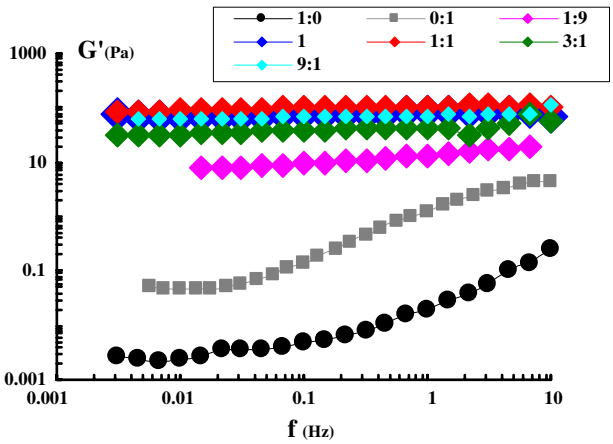


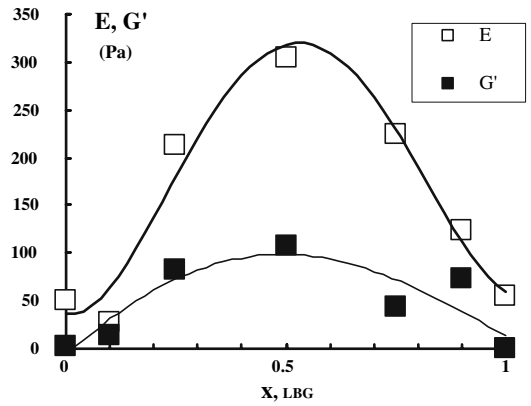
Fig. 6 Frequency dependence of storage modulus for LBG, Xanth, and LBG/Xanth at different weight ratios prepared at 75°C

of clarity only G′ values are reported in Fig. 6). The equilibrium shear moduli, Ge, have been also evaluated, assuming that they can be taken as the experimental values of G′ at 1 Hz (Lapasin and Pricl 1995). In Fig. 7, the Ge values are reported together with the Young moduli for the different LBG/Xanth systems. For a comparison also the G′ (1 Hz) and E values for the single polymers are given. It is interesting to note that both parameters assume the maximum values in the case of 1:1 sample and that, with the exception of the systems 1:9 and 9:1, the ratios of E/Ge are ca. 3, in agreement with the theory of the elasticity for isotropic viscoelastic solids at equilibrium (Ferry 1980).

Release studies from the LBG/Xanth matrices

The release from tablets of MGB, loaded in the hydrogel prepared with different LBG/Xanth weight ratios, was studied in distilled water at 37°C. The obtained results are reported in Table 3. The release of the model drug is almost negligible in the case of tablets prepared with only LBG due to the difficulty of the polymeric chains to dissolve in the surrounding medium. On the other side, in the case of Xanth, the release is rather fast because this polysaccharide is a polyelectrolyte that rapidly dissolves leading to a complete release of the MGB.

When the tablets were prepared with the hydrogels at different weight ratios, the release becomes deeply influenced by the co-presence of the two polymers: the release



X, LBG	0	0.1	0.25	0.50	0.75	0.90	1
E_{exp} (Pa)	0	28	212	304	224	125	54
E_{fit} (Pa)	36	64	179	317	228	112	60
G'_{exp} (Pa)	1	13	83	107	43	73	0
G'_{fit} (Pa)	0	31	73	98	72	39	13

Fig. 7 Dependence of the Young modulus (*open square*) and storage modulus G′ (*dark filled square*) on the weight composition of LBG/Xanth (X) samples prepared at 75°C. The fitting lines were drawn applying a polynomial equation of 4th order: the corresponding values, calculated at 1 Hz (G'_{fit}, E_{fit}), together with the experimental ones (G'_{exp}, E_{exp}) are also listed

after 8 h is always very small and also after 24 h reaches a maximum value of 15%, with only exception of the 1:9 LBG/Xanth where 44% of the drug is delivered after 24 h. These data indicate that, though the mechanical properties are very different depending on the different weight ratios (see Fig. 7), once the hydrogels are freeze-dried and compressed, the release behaviour is not simply related to such properties. The release appears to be essentially governed by LBG that, also when present in very small amount, does not allow the diffusion of the host molecule out of the matrices. Even when the LBG amount reaches 90%, more than half of MGB still remains entrapped in the tablets.

Conclusions

The mechanical properties of the gel systems, obtained by crosslinking carried out at different temperatures, are remarkably affected by reaction temperature and ageing time. The samples, kept at 37°C, show the maximum value of cohesion and hardness after 3 weeks. Later, the degradation processes prevail and the networks loose their consistency. The gel point could be detected by means of oscillatory tests: the evaluated critical exponent, $n = 0.46$, lies in the experimental range of already found values for several other systems. The disagreement with the percolation theory prediction and with the Rouse model is probably due to the fact that the gelation process takes place in the presence of an excess of the crosslinking agent. The tablets prepared with the chemical network evidenced the presence of meshes with a size large enough to release small molecules, leading to a delivery even faster than that obtained when only the non-crosslinked polymer was present. A different behaviour was observed in the case of larger guest molecules: the network acted as an obstacle to diffusion out of the matrix and the drug remained entrapped even after 1 day.

Furthermore, for the first time, the physical gels obtained by mixing, at different weight ratios, LBG and Xanth have been tested as matrices for drug release. Though the systems show remarkable differences in hardness and cohesion, the release profiles, when the hydrogels are used to prepare tablets, are not significantly different and usually only a small amount of the model drug is delivered. Only when Xanth is present with a percentage of 90%, the release becomes faster and a higher amount of MBG is released. Thus, the freeze-drying and compression processes reduce and smoothen the mechanical differences among the networks and the release appears to be governed essentially by the presence of LBG.

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