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New starch-based thermoplastic hydrogels for use as bone cements or drug-delivery carriers

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The development of new biodegradable hydrogels, based on corn starch/cellulose acetate blends, produced by free-radical polymerization with methyl methacrylate monomer (MMA) and/or an acrylic acid monomer (AA), is reported. The polymerization was initiated by a redox system consisting of a benzoyl peroxide and 4-dimethlyaminobenzyl alcohol at low temperature. These hydrogels may constitute an alternative to the materials currently used as bone cements or drug-delivery carriers. Swelling studies were carried out, as a function of pH and temperature, in buffered solutions. The xerogels were further characterized by Fourier transform–infrared spectroscopy. Tensile and compression tests, and dynamic mechanical thermal analysis were used to assess the mechanical performance of the developed materials. The fracture surfaces were observed by scanning electron microscopy. The developed materials are sensitive to the pH, showing a clear reversible transition in a relatively narrow interval of pH, which is just in the range of physiological conditions. These properties make the materials developed in this study very promising for biomedical applications. Fickian-type diffusion is the mechanism predominant in these systems, except for the composition with a higher concentration of AA, that corresponds to the most desirable kinetical behavior for controlled release (case II-transport mechanism). Furthermore, the results obtained in the mechanical tests are in the range of those reported for typical PMMA bone cements, showing that it is possible to develop partially degradable cements with an adequate mechanical behavior.

1. Introduction

The physical properties of hydrogels make them useful for a wide variety and growing number of biomedical applications, such as drug-delivery systems, ophthalmology and orthopaedics. Hydrogels are three-dimensional polymeric networks held together by cross-linked covalent bonds and weak cohesive forces in the form of either hydrogen bonds or ionic bonds [1–5]. Hydrogels are, by definition [6–7], a broad class of hydrophilic polymeric materials which have the inherent ability to swell in water and other suitable solvents, capable of imbibing and retaining more than 10% of their weight in water within the gel structure. Attributes such as permeability to small molecules (such as tissue metabolites), a soft consistency, and a low interfacial tension between the gel and an aqueous solution are some of the important properties which have helped to generate interest in hydrogels as useful biomaterials [2, 3, 5, 7, 8]. Additionally, the facility of purification, a high equilibrium water content (advantageous for the permeability and biocompatibility of these materials), along with their sterilizability makes them extremely versatile [2, 4]. The utility of hydrogels as biomaterials lies also in the similarity of their physical properties with those of living tissues [9].

Hydrogels can, for instance, be used as an interface between bone and an implant [2] with the aim of providing a mechanism for fixing a prosthesis in the intramedullary cavity. These novel cements would, in principle, dilate in a controlled manner by absorption of body fluids and achieve fixation by an expansion mechanism [2, 10]. In fact, a bone cement is frequently used to ensure a mechanical interlock between bone

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and joint prosthesis [2, 11] acting as an intermediary between the high-modulus prosthesis, and the low-modulus hard tissue, being designed to improve implant fixation [2, 12–14]. Biodegradable bone cements are highly desirable because they can provide for immediate structural support and, as they degrade from the site of application, they allow the ingrowth of new bone for complete healing of the bone fracture [15].

The physical properties of hydrogels make them also very useful for controlled-release applications, such as the delivery of contraceptives, opthalmics, antiarrhythmics, hormones, enzymes, anticancer agents, anticoagulants, antibodies, and antagonists [16]. Biodegradable polymers like poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymers, have recently found numerous applications in a variety of drug-delivery systems [17–22]. A potential alternative, for the currently used materials, is starch-based polymers which are well-known biodegradable materials [23, 24]. These materials have been very recently proposed for possible use as biomaterials [25–32]. Their good mechanical properties and appropriate degradation behavior [25, 27, 30] make them strong candidates for future biomedical applications. However, no study is available on their potential use as biomedical hydrogels.

This paper presents a preliminary study on the development of new hydrogels, based on corn starch/-cellulose acetate blends (SCA), produced by free-radical polymerization, aimed to be used as biodegradable bone cements or drug-delivery carriers. These biodegradable materials can provide immediate structural support, and promote the ingrowth of new bone as they are being degraded. Furthermore, in the case of drug-delivery systems, these materials eliminate the need for surgical removal of the device after drug depletion. The developed materials are sensitive to pH, showing a clear reversible transition in a relatively narrow interval of pH, which is just in the range of physiological conditions. This behavior makes these materials very promising for biomedical applications. The results obtained in swelling and mechanical tests showed that these partially biodegradable materials may present the required properties to be used as bone cements or drug-delivery carriers.

2. Materials and methods

The experimental hydrogels were formulated from commercially available corn starch/cellulose acetate thermoplastic blends (SCA, trade name Mater-Bi Y101U, Novamont, Novara, Italy) in the form of granules. These biodegradable materials have a starch content higher than 85% [23, 24]. The polymer granules were previously ground in a high-speed milling equipment to form SCA fine powder. Methyl methacrylate monomer (MMA, Merck, Germany), and acrylic acid monomer, (AA, Merck, Germany), were used as-received without further purification. The polymerization initiator was benzoyl peroxide (BPO, Merck), and it was purified by fractional recrystallization from ethanol, melting point 104 °C. The activator of the benzoyl peroxide initiator was one tertiary aromatic amine, a *N*-dimethylaminobenzyl alcohol, DMOH, that was previously synthesized by selective reduction of 4-dimethylaminobenzaldehyde with sodium borohydride in alkaline medium [33–36]. The solvent used, for some of the systems, was an ethanol/water solution (30/70 vol/vol).

The xerogels, that were aimed at being used as bone cements, were formulated by adding the liquid component to the solid component at room temperature. Four xerogels compositions (weight ratios) were investigated. The corresponding (wt/wt) ratios were 30/70; 40/60; 50/50; 60/40 of solid/liquid components. The solid component consisted of SCA powder to which the corresponding amount of finely ground BPO was added. A BPO concentration of 2% was used in all cases. The liquid component consisted of 32% AA (wt/wt) and 1% DMOH (wt/wt) for all compositions. The only formulation difference was the amount of MMA used, that depended on the solid/liquid relation. The MMA concentration used was 37%, 27%, 17% and 7% wt/wt, respectively.

In a second set of experiments, the xerogels (that were, in this case, aimed at being used as drug-delivery systems), were formulated without the presence of MMA monomer in the liquid. The liquid component consisted of AA previously added with 1% DMOH (wt/wt). An ethanol/water solution was added to the solid component in a 1:1 (wt/wt) ratios for all cases. Three xerogel compositions were investigated, with the following weight ratios of solid/liquid components: 15/85; 30/70; 50/50.

In order to characterize the swelling behavior of the hydrogels as a function of pH and temperature, equilibrium studies were performed. Xerogel rectangular samples (15 mm thick) were immersed, in buffered solutions of different pH, at different temperatures (25, 37 and 50 °C). The buffered solutions (Titrisol, Merck, Germany) pH ranged from 5–8. The swelling was followed by measuring the weight gain as a function of immersion time in 10 cm^3 buffered solution. Measurements were taken until equilibrium was reached, which was considered to happen when three consecutive determinations gave the same weight ($\pm$ 0.001 g). The developed materials were further characterized by Fourier Transformed Infrared Spectroscopy (FTIR), using a Perkin Elmer System 2000 FT-IR spectrometer, with a resolution of 4 cm^{-1}, and averaged over 32 scans. Xerogel samples were thoroughly ground with KBr and pellets were prepared by cold compression under vacuum.

Tensile and compressive characterization of the samples of the first system (containing MMA), were carried out on an Instron 4505 Universal Mechanical Testing Machine using a load cell of 50 kN. A crosshead speed of 5 mm min^{-1} (8.3×10^{-5} m s^{-1}) until 1% strain (for determining the modulus with higher precision) and then of 50 mm/min (8.3×10^{-4} m s^{-1}) until fracture was used in the tensile tests. A resistive extensometer (10 mm gage length) was used to measure strain with higher precision. These tests were used to determine the ultimate tensile strength, (UTS), and the secant modulus at 1% strain. Compression

testing was carried out at a crosshead speed of 2 mm min^{-1} (4.7×10^{-5} m s^{-1}), up to fracture or until obtaining a maximum reduction in samples height of 60%. The samples for these tests were prepared by placing the cement dough in poly(tetrafluoroethylene) (PTFE) molds. These tests were used to determine the ultimate tensile strength, UTS, and the secant modulus at 1% strain, E_C. The samples were then stored under controlled environmental conditions (23 °C; 55% RH) until mechanical testing. The average cross-sections of the samples were 60 mm × 5 mm for tensile tests (dumb-bell samples) and 12 mm height and 6 mm diameter for the compressive tests. A minimum of eight samples were tested for each composition. Fracture surfaces were observed by scanning electron microscopy (SEM) in a Leica Cambridge S360 microscope.

Dynamic mechanical thermal analysis (DTMA) was also used for characterizing the mechanical behavior of these materials. These tests were carried out using a three-point bending solicitation scheme, by means of scanning the temperature from −20 to 160 °C, in a Perkin–Elmer 7 Series Thermal Analysis System (specimen size 20 mm × 5 mm × 3 mm). Two distinct frequencies (1 and 10 Hz) were studied. A constant heating rate of 4 °C min^{-1} was used in all the tests.

3. Results and discussion

3.1. Swelling behavior

Swelling characteristics of a polymer are of utmost importance in biomedical and pharmaceutical applications because the equilibrium degree of swelling influences: (i) the solute diffusion coefficient through these hydrogels, (ii) the surface properties and surface mobility, and (iii) its mechanical properties [4]. Consequently, for biomedical applications such as implants and drug-delivery systems, it is very important to determine the water absorption capacity of these materials at different pHs and temperatures. The water uptake, W, was calculated using the following equation

$$W = \frac{M - M_0}{M_0} = \frac{M}{M_0} - 1 \quad (1)$$

where M_0 is the weight of dry sample (xerogel) and M is weight of the sample at time t. The maximum value of water uptake was considered as the equilibrium water uptake, W_{eq}, which was obtained after 24 h immersion for the systems with MMA, and 7 h for the systems without MMA.

The equilibrium water uptake of SCA, determined at 37 °C for a pH = 7, was 0.63. This high value is practically equal for different pHs and similar to that obtained for amylopectin by other authors [37]. This can be easily explained by the fact that SCA is mainly constituted by corn starch (> 85%) which is basically composed of amylopectin (72%) [38]. The highly branched structure of amylopectin, together with the greater amount of hydroxilic groups present on its structure (on which the water molecules can be retained) may also contribute to the high value of the equilibrium water uptake.

TABLE I Equilibrium water content, W_{eq} (g H_2O/g polymer) of different systems at 25 °C as a function of pH

Solid/liquid ratios (wt/wt)	MMA content (%)	pH			
		5	6	7	8
30/70	37	0.3462	0.5091	0.7321	0.4152
40/60	27	0.3542	0.3644	0.5741	0.3872
50/50	17	0.3451	0.3715	0.4165	0.3768
60/40	7	0.3629	0.3511	0.3965	0.3684
15/85	–	9.0662	11.2055	10.3696	3.001
30/70	–	1.0504	1.3326	1.0857	0.7427
50/50	–	0.4663	0.5499	0.4655	0.4501

TABLE II Equilibrium water content, W_{eq} (g H_2O/g polymer) of different systems at 37 °C as a function of pH

Solid/liquid ratios (wt/wt)	MMA content (%)	pH			
		5	6	7	8
30/70	37	0.3550	0.4430	0.7661	0.4167
40/60	27	0.3757	0.4544	0.5391	0.4163
50/50	17	0.3995	0.4040	0.4428	0.41
60/40	7	0.3669	0.3538	0.4366	0.4011
15/85	–	7.4795	10.50	14.5488	3.4656
30/70	–	0.8618	2.88	0.8644	0.7601
50/50	–	0.6164	0.97	0.6454	0.5240

TABLE III Equilibrium water content, W_{eq} (g H_2O/g polymer) of different systems at 50 °C as a function of pH

Solid/liquid ratios (wt/wt)	MMA content (%)	pH			
		5	6	7	8
30/70	37	0.3888	0.6779	1.1526	0.4981
40/60	27	0.3918	0.5551	0.656	0.4868
50/50	17	0.4208	0.6575	0.6811	0.4777
60/40	7	0.4172	0.4695	0.5457	0.4574
15/85	–	6.6725	8.119	7.5678	3.8453
30/70	–	0.3981	0.6037	0.9387	0.577
50/50	–	0.5454	0.5022	0.6065	0.5761

The equilibrium water uptake of these hydrogels increased for higher amounts of MMA and AA monomers in the network at different temperatures (Tables I, II and III). This increase is higher for the hydrogels composed only by AA monomer, which is an anionic monomer and therefore very hydrophilic. The higher equilibrium water uptake for the hydrogels with greater contents of the MMA monomer, (hydrophobic monomer), may be due to the low degree of cross-linking of these hydrogels or to the higher concentrations of pores (or defects) in the material, where the water fills these defects.

The developed materials are sensitive to the pH, showing a clear reversible transition in a relatively narrow interval of pH, which is in the range of physiological conditions (Fig. 1). In the hydrogels without MMA monomer, only the formulation with higher concentration of AA monomer is pH sensitive (Fig. 2). The others compositions hardly show any changes at the different pHs.

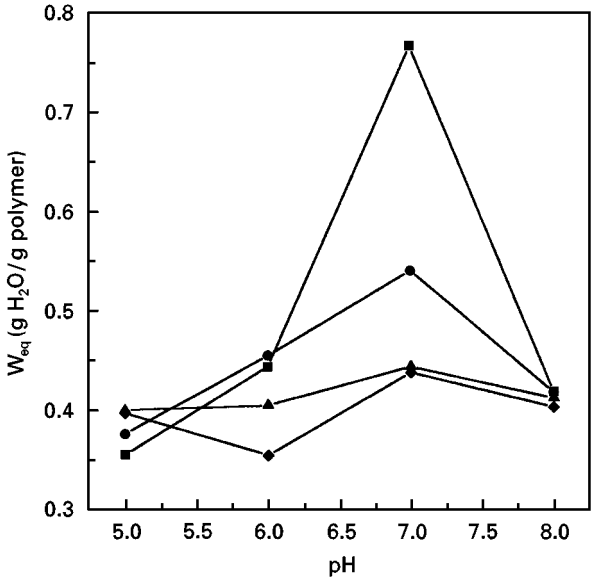

Figure 1 Variation of the equilibrium water uptake as a function of buffered solution pH for different compositions of SCA/AA/MMA systems at 37 °C: (■) 37% MMA, (●) 27% MMA, (▲) 17% MMA and (◆) 7% MMA.

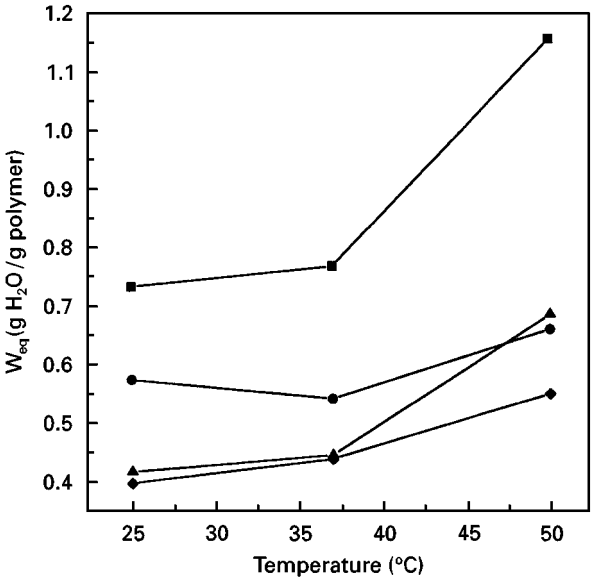

Figure 3 Variation of the equilibrium water uptake as a function of temperature for different compositions of SCA/AA/MMA systems at pH = 7: (■) 37% MMA, (●) 27% MMA, (▲) 17% MMA and (◆) 7% MMA.

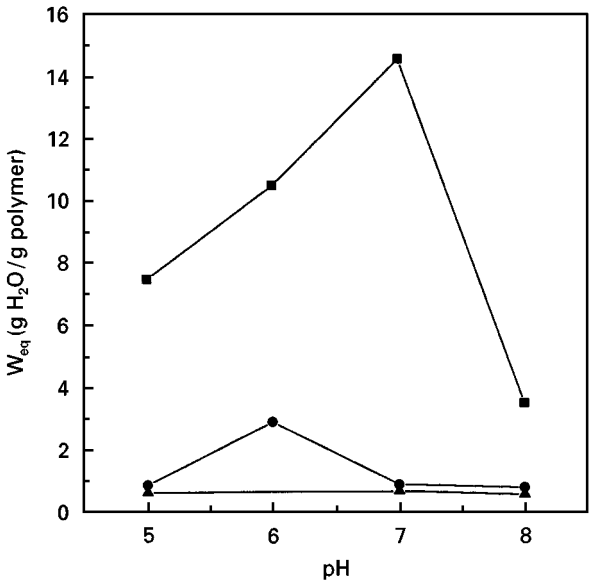

Figure 2 Variation of the equilibrium water uptake as a function of buffered solution pH for different compositions (solid/liquid ratios) SCA/AA systems at 37 °C: (■) 15/85, (●) 30/70 and (▲) 50/50.

TABLE IV Diffusional exponent n (calculated from Equation 2) for water transport in different compositions with MMA in buffer solutions at 37 °C

pH buffer	n			
	MMA = 7%	MMA = 17%	MMA = 27%	MMA = 37%
5	0.50 ± 0.01	0.49 ± 0.02	0.50 ± 0.01	0.48 ± 0.20
6	0.48 ± 0.01	0.48 ± 0.05	0.52 ± 0.05	0.63 ± 0.02
7	0.48 ± 0.03	0.57 ± 0.02	0.59 ± 0.03	0.60 ± 0.02
8	0.54 ± 0.01	0.58 ± 0.02	0.55 ± 0.02	0.55 ± 0.01

TABLE V Diffusional exponent n (calculated from Equation 2) for water transport in different compositions without MMA in buffer solutions at 37 °C (solid/liquid ratios, wt/wt)

pH buffer	n		
	15/85 wt/wt	30/70 wt/wt	50/50 wt/wt
5	0.68 ± 0.02	0.61 ± 0.02	0.53 ± 0.01
7	0.93 ± 0.02	0.60 ± 0.02	0.49 ± 0.01
8	0.92 ± 0.01	0.56 ± 0.02	0.46 ± 0.08

The data indicate that swelling capability increases with temperature, particularly for the compositions with MMA (Fig. 3).

To elucidate the transport mechanism, the initial swelling data are fitted using the following equation [39]

$$\frac{M_t}{M_{eq}} = Kt^n \tag{2}$$

where M_t is the mass of water uptake at any time t, M_{eq} is the equilibrium water uptake, and K and n are constants. These constants are characteristic parameters of the specific (bioactive agent)/(dissolution medium) system.

A value of $n = 0.5$ indicates Fickian diffusion and a value of $n = 1$ implies case II transport; values of n between these limits define anomalous or non-Fickian transport, where both diffusion and polymer relaxation control simultaneously the overall rate of water uptake. The values of the diffusion exponent n are presented for a 95% confidence level.

The values of n are reported in Tables IV and V. Fickian transport ($n = 0.5$) was observed for all the polymer formulations containing MMA (Table IV), except for the composition with higher MMA content at pH = 6 and 7. This indicates that water transport mechanism becomes non-Fickian for these pH values.

Figure 4 FT–IR spectra for the original SCA blend and for the different compositions (solid/liquid ratios) within the SCA/AA systems: (a) SCA, (b) 15/85, (c) 30/70 and (d) 50/50.

For the compositions without MMA (Table V), it was found that n increased as the AA monomer content increased. This indicates that the water-transport mechanism becomes non-Fickian and case II transport ($n \approx 1$) was observed for the composition with higher concentration of AA, which corresponds to the most desirable kinetical behavior for a swelling-controlled release material. The water transport mechanism seems to deviate much more from the Fickian mechanism in compositions without MMA monomer, which can be explained by the hydrophobic character of the α-methyl group of MMA.

3.2. FT–IR characterization

Figs 4 and 5 show the FT–IR spectra of the composites containing either AA or mixtures of AA-MMA, respectively, along with that of the starch-based blend, SCA. The composite systems present a signal wider than the corresponding original polymeric components which could indicate some interactions between the two components (SCA and AA) as well as the possible formation of grafted chains. Wide signals centered at 3435 cm^{-1} are assigned to the poly(acrylic acid) chains (grafted and ungrafted) into the polysaccharide chains. The acetate group of the SCA component gives a relatively small signal at 1755 cm^{-1} assigned to the carbonyl ester group, whereas the carboxylic acid gives a stronger signal centered at 1730 cm^{-1}. Finally, the signals at 1155, 1075 and 1030 cm^{-1} have been clearly associated with the O–C bonds of the SCA macromolecules, as has been reported for other polysaccharides.

Although the FT–IR results are not conclusive on their own, it seems to indicate the strong hydrogen-bonding interactions of both polymeric components, as well as the possible formation of a fraction of grafted copolymer chains. In the case of the MMA system it is necessary to take into consideration the formation of a copolymer of AA and MMA units according to the initial composition of reagents. In this case the carbonyl ester groups give a relatively narrow signal at 1735 cm^{-1} shifted with respect to that of the acetate group of SCA macromolecules. The signals at 1155 and 1030 cm^{-1} of the carbohydrate are even better defined than in the case of the AA–SCA polymeric systems. It is clear from the analysis of those spectra that the developed systems present less interactions between both components of AA–MMA units into the SCA chains than could be expected.

3.3. Mechanical properties

The results of the tensile and compression tests are summarized in Table VI. The obtained mechanical properties are in range of those reported for a typical PMMA bone cement [40], namely a strength of 65–100 MPa (compression) and 20–35 MPa (tensile) and a modulus of 1.5–3.0 GPa (compression) and 3.0–5.0 GPa (tensile).

Scanning electron micrographs of the obtained fracture surface are shown in Fig. 6a–d. These materials present a brittle fracture which is also typical of the conventional PMMA cements [41]. In these pictures one can observe the presence of porosity which increases with the amount of MMA monomer. This

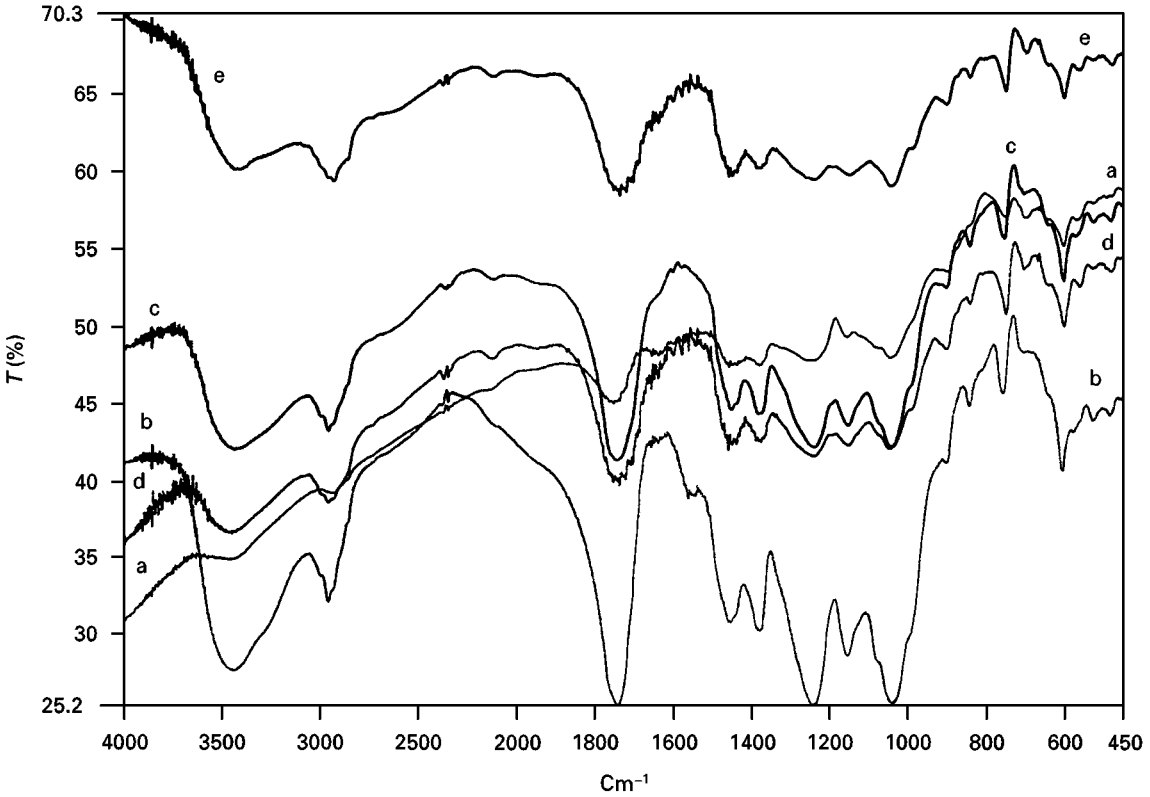

Figure 5 FT–IR spectra for the original SCA blend and for the different compositions within the SCA/AA/MMA systems: (a) SCA, (b) 37% MMA, (c) 27% MMA, (d) 17% MMA and (e) 7% MMA.

TABLE VI Mechanical properties of the different compositions with MMA

Material	F_T[b] (GPa)	UTS_T[b] (MPa)	F_C[c] (GPa)	UTS_C[c] (MPa)
30/70[a] (37% MMA)	3.82 ± 0.88	20.63 ± 1.46	1.46 ± 0.28	45.05 ± 11.5
40/60[a] (27% MMA)	3.02 ± 0.21	22.07 ± 3.28	1.30 ± 0.66	88.68 ± 12.30
50/50[a] (17% MMA)	3.23 ± 0.51	28.51 ± 2.87	1.66 ± 0.24	84.09 ± 17.80
60/40[a] (7% MMA)	2.53 ± 0.34	25.99 ± 2.90	1.3 ± 0.36	97.62 ± 10.80

[a]Solid/liquid component.
[b]T, tensile.
[c]C, compression.

porosity will obviously influence the mechanical properties (it may cause for instance a 50% reduction in impact and flexural strength) [42]. However, it may be argued that the presence of pores may have either a positive or a negative effect [13, 14, 43]. It is intuitively expected that pores would act as stress risers (local points for stress concentration) and nucleation site for cracks, rendering the cement susceptible to early fatigue fracture. On the other hand, pores may serve to blunt propagating cracks [13, 14, 43]. These porous structures may be produced as a result of the entrapment of air bubbles during the manual mixing of the power and liquid components (which can be further improved), by release of absorbed air during polymerization, and, if the temperature of polymerization is high enough, by vaporization of the monomer. An increased amount of liquid component increases the maximum temperature, that can be related with high porosity of the composition with 70% of the component liquid (Fig. 6d).

For higher concentrations of SCA, this polymer may be clearly distinguished in the matrix (Fig. 6a and b). That means that SCA powder dissolves only partially into the liquid monomers. Consequently, these amounts may be responsible for the initiation of the crack propagation on the biomaterial interfaces or in the bulk of the cement layer. Again, this tends to indicate that the manufacturing procedures of the hydrogels should be improved in coming studies.

The dynamic–mechanical spectrum of the compositions with MMA are shown in Fig. 7. The glass transition temperatures T_gs (or α relaxation), of the

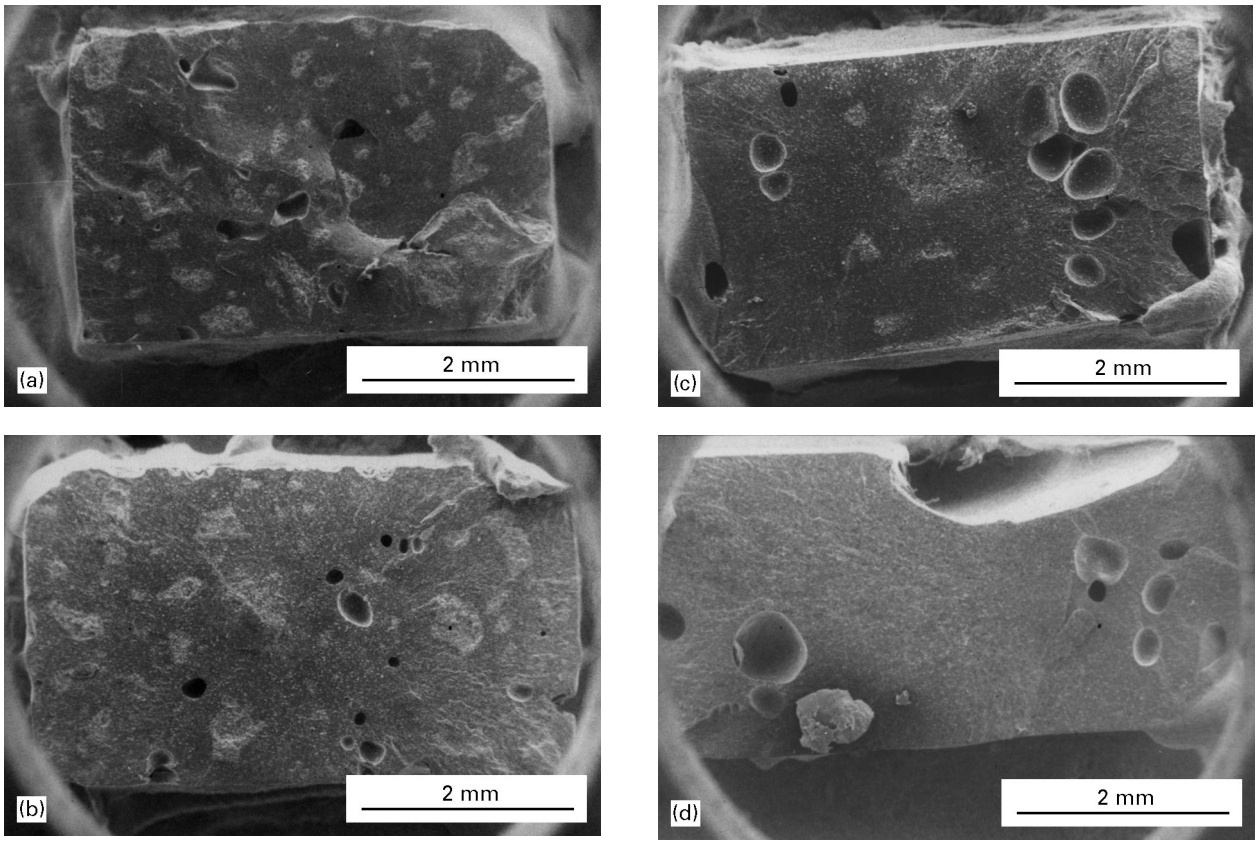

Figure 6 Scanning electron micrographs of tensile fracture surfaces for the different studied compositions (solid/liquid ratios) containing MMA: (a) 7% MMA (60/40), (b) 17% MMA (50/50), (c) 27% MMA (40/60) and (d) 37% MMA (30/70).

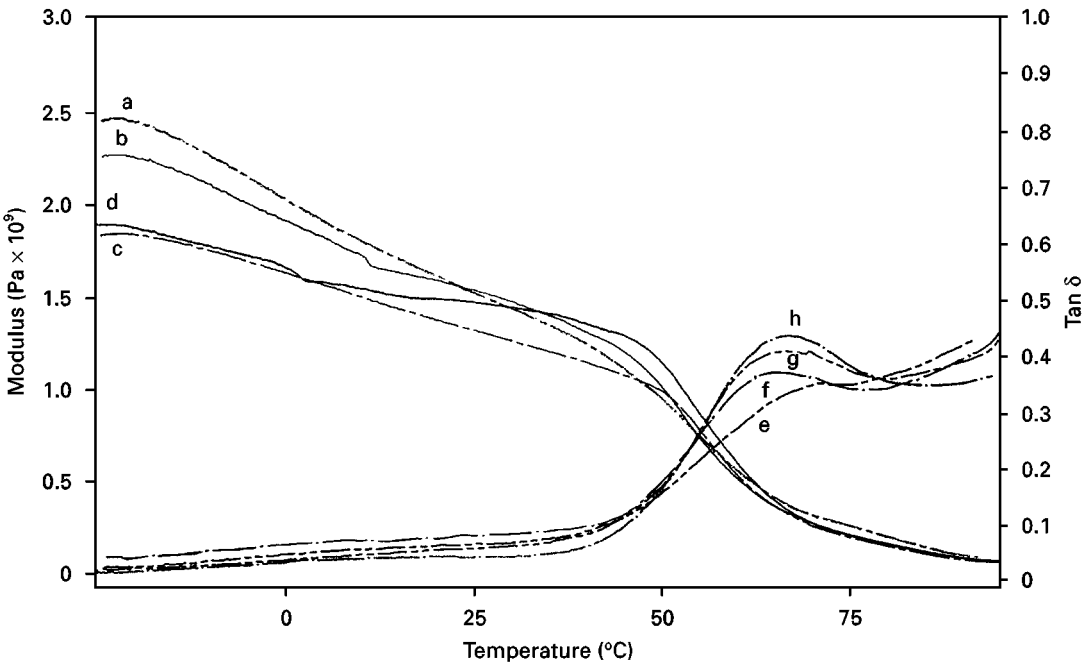

Figure 7 DMTA spectra for the different compositions of the SCA/AA/MMA systems tested at a frequency of 1 Hz: (a) storage modulus of the composition with 7% MMA, (b) storage modulus of the composition with 17% MMA, (c) storage modulus of the composition with 27% MMA, (d) storage modulus of the composition with 37% MMA, (e) tan δ of the composition with 7% MMA, (f) tan δ of the composition with 17% MMA, (g) tan δ of the composition with 27% MMA and (h) tan δ of the composition with 37% MMA.

cements were read off as the temperatures at which the loss modulus or loss factor passed through a maximum [44]. The higher concentration of monomers exerts a plasticizing effect on the polymer, lowering its glass transition temperature and also reducing the modulus. The materials developed in this study present higher values of dynamic modulus with increasing frequency (Fig. 8), similar to the behavior exhibited by bulk polymerized poly(methyl methacrylate) [44]. The T_g of these materials also increased with

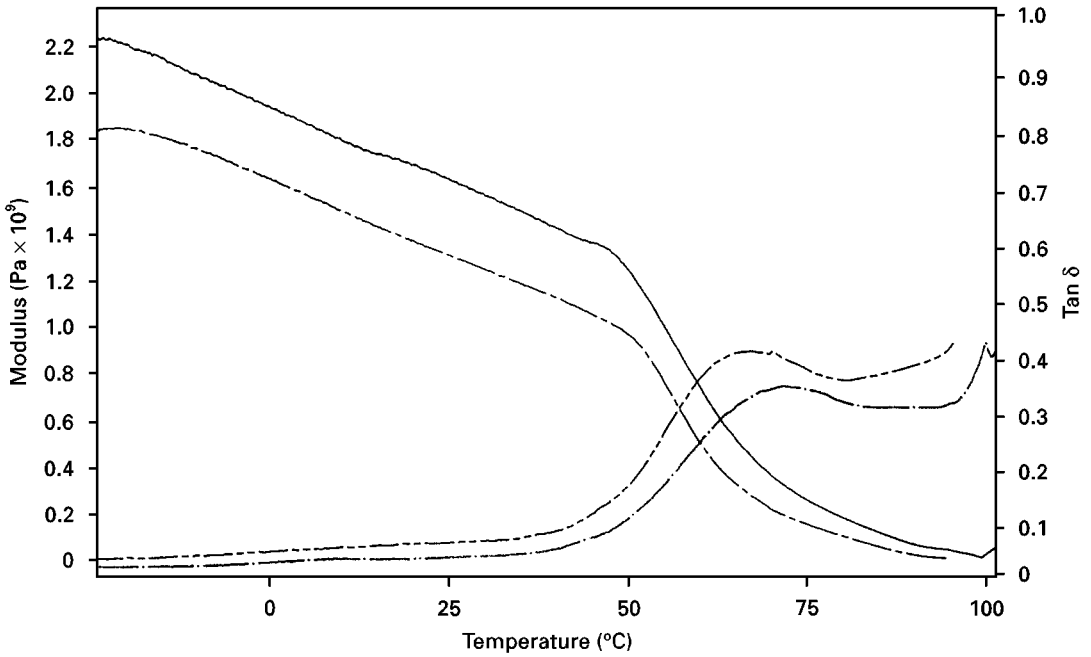

Figure 8 DMTA spectra for the composition of 40/60 solid/liquid ratio (17% MMA) tested at frequency of 1 and 10 Hz, (—) storage modulus at frequency of 10 Hz, (—·—) tan δ at frequency of 10 Hz, (—-—) storage modulus at frequency of 1 Hz, and (—--—) tan δ at frequency of 1 Hz.

frequency, as well as the corresponding width of peaks, indicating a broader distribution of relaxation times.

4. Conclusion

Novel hydrogels based on starch blends, that present a very interesting combination of properties which may allow for their use as bone cements or as drug-delivery carriers, were developed. These materials present a very useful transition (pH effect) just in the range of physiological conditions, which may offer enormous possibilities in the field of biomedical applications. Fickian-type diffusion is the mechanism predominant in these hydrogels, except for the composition with a higher concentration of AA, that corresponds to the most desirable kinetic behavior for a swelling-controlled release (case II transport mechanism). This result may be very useful in controlled releasing of drugs or bioactive agents. The swelling behavior of these materials compensates for the volume shrinkage which occurs during polymerization, which can provide for a mechanism for fixing a prosthesis in the intramedullary cavity. Furthermore, the mechanical properties are in the range of those reported for a typical PMMA bone cement, which may allow their future use as partially degradable *in situ* polymerized cements.

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References

1. N. A. PEPPAS and A. G. MIKOS, in "Hydrogels in Medicine and Pharmacy-Fundamentals", Vol. I, edited by N. A. Peppas (CRC Press, Boca Raton, FL, 1988) p. 1.
2. P. A. NETTI, J. C. SHELTON, P. A. REVELL, C. PIRIE, S. SMITH, L. AMBROSIO, L . NICOLAIS and W. BONFIELD, *Biomaterials* **14** (1993) 1098.
3. S. WOERLY, *ibid.* **14** (1993) 1056.
4. N. A. PEPPAS, in "Biomaterials Science – An Introduction to Materials in Medicine-Part I", edited by B. D. Ratner, A. S. Hoffman, F. J. Schoen and J. E. Lemons (Academic Press, London, 1996) p. 60.
5. B. PASCUAL, I. CASTELLANO, B. VÁZQUEZ, M. GURRUCHAGA and I. GOÑI, *Polymer* **37** (1996) 1005.
6. E. J. MACK, T. OKANO and S. W. KIM, in "Hydrogels in Medicine and Pharmacy-Polymers", Vol. II, edited by N. A. Peppas (CRC Press, Boca Raton, FL, 1988) p. 65.
7. E. KARADAG, D. SARAYDIN, S. ÇETINKAYA and O. GUVEN, *Biomaterials* **17** (1996) 67.
8. S. W. KIM, Y. H. BAE and T. OKANO, *Pharmaceut. Res.* **9** (1992) 283.
9. M. D. BLANCO, O. GARCÍA, R. M. TRIGO, J. M. TEIJON and I. KATIME, *Biomaterials* **17** (1996) 1061.
10. A. ABUSAFIEH, S. SIEGLER and S. R. KALIDINDI, *J. Biomed. Res.* **38** (1997) 314.
11. T. L. NORMAN, V. KISH, J. D. BLAHA, T. A. GRUEN and K. HUSTOSKY, *J. Biomed. Mater. Res.* **29** (1995) 495.
12. J. YANG, *Biomaterials* **18** (1997) 1293.
13. G. LEWIS, J. S. NYMAN and H. H. TRIEU,, *J. Biomed. Mater. Res.* **38** (1997) 221.
14. G. LEWIS, *ibid.* **38** (1997) 155.
15. A. J. DOMB, N. MANOR and O. ELMALAK, *Biomaterials* **17** (1996) 411.
16. J. KOST and R. LANGER, in "Hydrogels in Medicine and Pharmacy-Properties and Applications", Vol. III, edited by N. A. Peppas (CRC Press, Boca Raton, FL, 1988) p. 95.
17. D. LOHMANN, *Macromol. Symp.* **100** (1995) 25.
18. Y. OGAWA, *J. Biomater. Sci. Polymer Edn* **8** (1997) 391.
19. L. DI SILVIO, N. GURAV, M. V. KAYSER, M. BRADEN and S. DOWNES, *Biomaterials* **15** (1994) 931.
20. A. G. ANDREOPOULOS, *Clin. Mater.* **15** (1994) 691.
21. R. LANGER, *MRS Bull.* (1995) 18.

22. J. HELLER, in "Applications of Materials in Medicine and Dentistry-Part II", edited by B. D. Ratner, A. S. Hoffman, F. J. Schoen and J. E. Lemons (Academic Press, London, 1996) p. 346.
23. C. BASTIOLI, in "Recycle'94 – Davos Global Forum and Exposition", Switzerland, March 1994.
24. *Idem*, in "Degradadble Polymers-Principles and Applications" (Chapman and Hall, London, 1995) p. 112.
25. R. L. REIS, A. M. CUNHA, *J. Mater. Sci. Mater. Med.* **6** (1995) 786.
26. R. L. REIS, A. M. CUNHA, P. S. ALLAN and M. J. BEVIS, *Polym. Adv. Technol.* **7** (1996) 784.
27. R. L. REIS, S. C. MENDES, A. M. CUNHA and M. J. BEVIS, *Polym. Int.* **43** (1997) 347.
28. R. L. REIS, A. M. CUNHA, P. S. ALLAN and M. J. BEVIS, *Adv. Poly. Technol.* **16** (1997) 263.
29. R. L. REIS, A. M. CUNHA and M. J. BEVIS, *Med. Plast. Biomateri.* (1997) 46.
30. C. S. PEREIRA, M. E. GOMES, R. L. REIS and A. M. CUNHA, in "Foams, Emulsion and Cellular Materials", edited by J. F. Sadoc and N. River (NATO/ASI series, Kluwer Press, Dordrecht, 1998) in press.
31. R. L. REIS and A. M. CUNHA, in "Antec'98-Plastics on My Mind", Society of Plastics Engieers, Atlanta, April/May 1998, in press.
32. *Idem*, *ibid*.
33. C. ELVIRA, B. LEVENFELD, B. VÁZQUEZ and J. SAN ROMÁN, *J. Polym. Sci. A Polym. Chem.* **34** (1996) 2783.
34. P. A. LISO. B. VÁZQUEZ, M. REBUELTA, M. L. HERNÁEZ, R. ROTGER and J. SAN, *Biomaterials* **18** (1997) 15.
35. B. VÁZQUEZ, C. ELVIRA, B. LEVENFELD, B. PASCUAL, I. GOÑI, M. GURRUCHAGA, M . P. GINERBA, F. X. GIL, J. A. PLANELL, P. A. LISO, M. REBUELTA and J. SAN RÓMAN, *J. Biomed. Mater. Res.* **34** (1997) 129.
36. B. VÁZQUEZ, C. ELVIRA, J. SAN ROMÁN and B. LEVENFELD, *Polymer* **38** (1997) 4365.
37. I. CASTELLANO, B. PASCUAL, B. VÁZQUEZ, I. GOÑI and M. GURRRUCHAGA, *J. Appl. Polym. Sci.* **54** (1994) 577.
38. J. JANE, *J.M.S. Pure Appl. Chem.* **A32** (1995) 751.
39. N. A. PEPPAS and R. W. KORSMEYER, in "Medicine and Pharmacy-Properties and Applications", Vol. III, edited by N. A. Peppas (CRC Press, Boca Raton, FL, 1988) p. 109.
40. S. SAHA and S. PAL, *J. Biomed. Mater. Res.* **18** (1984) 435.
41. E. P. LAUTENSCHLAGER, B. K. MOORE and C.M. SCHOENFELD, *J. Biomed. Mater. Res. Symp.* (1974) 185.
42. C. MIGIARESI, L. FAMBRI and J. KOLANIK, *Biomaterials* **15** (1994) 875.
43. L. D. T. TOPOLESKI, P. DUCHEYNE and J. M. CUCKLER, *ibid.* **14** (1993) 1165.
44. R. L. CLARKE, *ibid.* **10** (1989) 494.

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