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Complexation of polymeric drugs based on polyacrylic chains with aminosalicylic acid side groups

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Polymeric drugs and ionomers can exhibit properties associated with the polymeric nature, such as adhesion, or coating of different substrates by polymeric active films, and can be applied successfully in the field of biomaterials. In this sense, complexation with calcium ions of two polyacrylic systems derived from 4-aminosalicylic acid (poly (4-HMA)), and 5-aminosalicylic acid, (poly (5-HMA)), have been studied by Fourier transform–infrared spectroscopy and thermogravimetric analysis. Both techniques support the ability of these polymers to form complexes with calcium ions as polycarboxylates.

1. Introduction

After the development of polyalkenoate cements by Wilson and Kent in 1971 [1, 2], several groups have devoted much attention to the study and preparation of polyelectrolyte complexes formed by the ionic interaction of polycarboxylic acids with divalent cations such as Ca^{2+}, Mg^{2+}, Zn^{2+}, trivalent Al^{3+}, and other metallic salts of iron, cobalt, etc. [3, 4]. This kind of complex has found interesting applications in dentistry and filling materials for bone fracture and bone regeneration [5, 6], as well as in the design and application of specific drug-delivery systems [7, 8]. The participation of Ca^{2+} ions in the formation of ionic complexes with polycarboxylic acids, is of great importance for applications in contact with bone tissue because of the enormous influence of calcium in all the remodelling process of the human skeleton, including the natural loosening of osseous mass associated with osteoporotic disease.

The complexation ability of salicylic acid derivatives is well documented in the literature [9, 10]. The *ortho* position of the hydroxylic and carboxylic groups of the aromatic ring gives the most adequate geometry and spatial configuration for the formation of intermolecular chelates and intramolecular complexes with polyvalent cationic ligands [9, 10]. Therefore, it is interesting to study the formation and properties of complexes of polymeric derivatives of salicylic acid with calcium salts. This work deals with the synthesis of two polymeric acrylic systems supporting isomeric derivatives of the aminosalicylic acid, as well as the analysis of their complexes with calcium ions. These systems offer interesting applications in the field of bone cements with a double function as calcium complexing compound, and as analgesic and anti-inflammatory drugs associated with specific functions of the salicylic groups.

2. Materials and methods

The monomers 4-HMA and 5-HMA are methacrylamides derived from 4-amino and 5-amino salicylic acid, respectively [1]. Poly (4-HMA) and poly (5-HMA) (see Fig. 1), were synthesized by the free-radical polymerization of the corresponding methacrylic monomers, in dimethylformamide solution at 50 °C using azobis *iso*butyronitrile (AIBN), as free-radical initiator. High molecular weight polymers were isolated by precipitation in a large excess of diethyl ether. More details on the synthesis and characterization of these polymers are described elsewhere [11].

Complexation studies with calcium ions of both polymers were carried out by Fourier transform– infrared FT–IR spectroscopy and thermogravimetric analysis (TGA). The complexation process was carried out according to the following protocol: to a solution of dimethylformamide/water (1 : 1) of 100 mg of the corresponding polymer, an equimolecular amount of an aqueous solution of Cl_2Ca (396 mg in 20 ml H_2O) was added with constant stirring. The precipitates were filtered and vacuum dried over phosphorus pentoxide. Salicylic acid was treated in a similar manner for comparative studies.

2.1. Spectroscopic analysis

FT–IR spectra were recorded using a Nicolet 520 spectrometer with a resolution of 4 cm^{-1} and averaged

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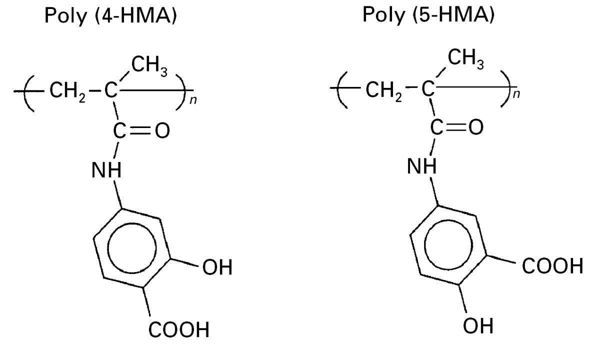

Figure 1 Chemical structure of poly (4-HMA) and poly (5-HMA).

over 32 scans. Samples were thoroughly ground with KBr and pellets were prepared by compression under vacuum.

2.2. Thermogravimetric analysis

Polymers (5–7 mg) and the corresponding calcium salts were analysed using a thermogravimetric analyser TGA-7, Perkin–Elmer, under a nitrogen atmosphere and at a constant heating rate of 10 °C min^{-1}. Loss of weight and the corresponding differential curves were registered in the thermograms.

3. Results and discussion

Poly (4-HMA) and poly (5-HMA) (Fig. 1), are two isomeric polymethacrylamides with different relative orientation of the salicylic acid side group with respect to the methacrylamide function. The orientation associated with the interchanged position of the –OH and the –COOH groups of the salicylic side group, gives different characteristic properties such as the isotacticity parameters of the polymers, as well as different glass transition temperatures, showing a higher stiffness in the case of poly (5-HMA).

The calcium complexation studies of both systems were accomplished by FT–IR spectroscopy. Spectra of the compounds are given in Figs 2–4, and the most significant peak positions are tabulated in Table I.

3.1. Hydroxyl and carboxylic–OH bands

A broad band between 3550–2400 cm^{-1} can be observed for the two polymeric systems (Figs 2a and 3a), which corresponds mainly to the stretching vibration of the carboxylic–OH, but also to the phenolic and to the –NH– of the amide stretching vibrations, in the 3000 cm^{-1} range. The possibility of the polymer systems to form intra- and intermolecular hydrogen bonds between the phenolic and the carboxylic groups, shows the absence of a typical band for free bonded hydroxyl groups. The salicylic acid FT–IR spectrum (Fig. 4a) shows a broad band between 3300 and 2400 cm^{-1} assigned to the carboxylic –OH stretching vibration, in which at 3240 cm^{-1} can be observed a sharp band corresponding to the phenolic –OH group intramolecularly bonded to the carboxylic function.

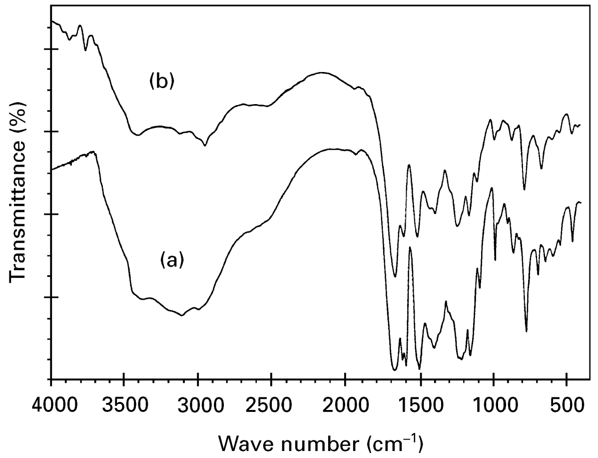

Figure 2 FT–IR spectra of (a) poly (4-HMA), and (b) poly (4-HMA) after treatment with Cl_2Ca (poly-4-HMACa).

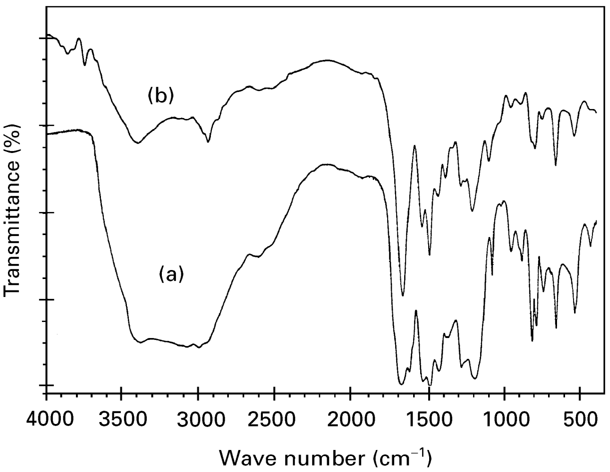

Figure 3 FT–IR spectra of (a) poly (5-HMA) and (b) poly (5-HMA) after treatment with Cl_2Ca (poly-5-HMACa).

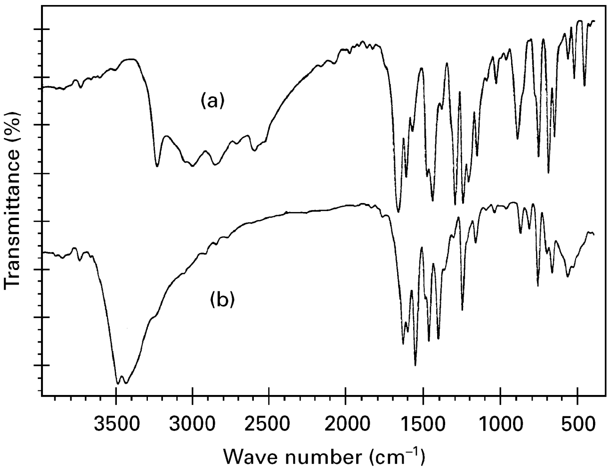

Figure 4 FT–IR spectra of (a) salicylic acid, and (b) salicylic acid after treatment with Cl_2Ca.

After treating the systems with Cl_2Ca, the formation of the corresponding calcium salts (poly-4HMACa and poly-5HMACa) is expected. The polymer spectra (Figs 2b and 3b) show a large decrease in the band intensity which can be attributed to the calcium carboxylate formation. On the other hand, the spectrum

TABLE I The most significant FT–IR band positions of the pure polymers, salicylic acid, and the corresponding carboxylates after treatment with Cl_2Ca

Peak assignment (cm^{-1})	Poly (4-HMA)	Ca poly (4-HMA)	Poly (5-HMA)	Ca poly (5-HMA)	Salicylic acid	Salicylic acid Ca
–OH stretch (carboxylic and hydroxyl)	3650–2400 Broad	3650–2400	3650–2400 Broad	3650–2400	3300–2400 Broad	3486–3437
Carboxylic C = O stretch	1679 Broad	1665	1672 Broad	1665	1665	1630
Carboxylic C–O stretch	1222	1236	1208	1215	1240	1250

of salicylic acid treated with Cl_2Ca, (Fig. 4b), shows typical bands of free bonded –OH, indicating the absence of hydrogen bonding with the carboxylic groups, and the calcium carboxylate formation.

3.2. Carboxylic carbonyl bands

The amide and the carboxylic functions present in the polymeric systems, show a broad band at 1679 cm^{-1} for poly (4-HMA) and at 1672 cm^{-1} for poly (5-HMA), corresponding to the carbonyl stretching vibrations of these groups (Figs 2a and 3a). After treatment with Cl_2Ca, the polymer spectra show narrower bands, and the wave number decreases to the corresponding carbonyl stretching vibrations to 1665 cm^{-1} in both cases (Figs 2b and 3b).

The same behaviour is observed when salicylic acid was treated with the calcium solution, whereas the carbonyl band shifts from 1665 cm^{-1} for pure salicylic acid, to 1630 cm^{-1} for the calcium-treated salicylic acid (Fig. 4a and b). In this sense, the decrease in wave number of the carboxylic carbonyl bands is in accordance to the formation of the carboxylate ionic complexes after treating the polymers and the salicylic acid with Cl_2Ca [2], possibly forming a carboxylate complex in which two carboxylic units are involved (Fig. 5).

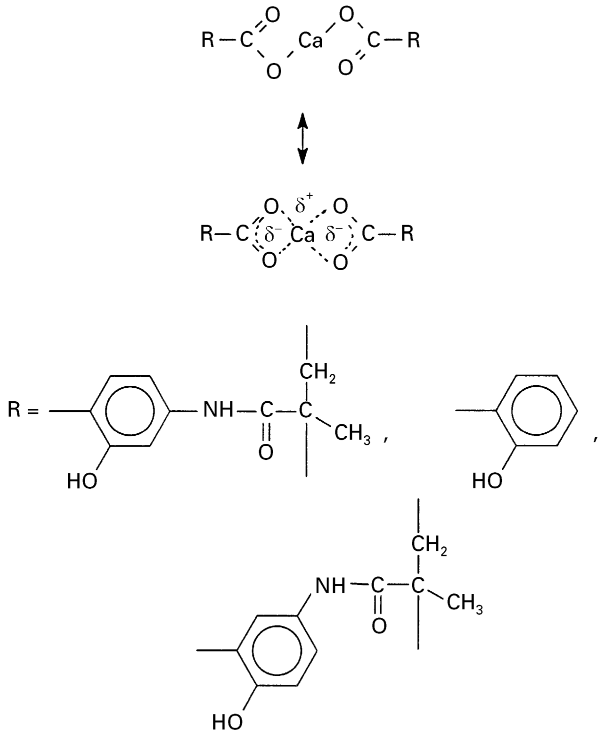

Figure 5 Calcium carboxylate formation after treating poly (4-HMA), poly (5-HMA) and salicylic acid, with Cl_2Ca, (structures involving carboxylate units, resonance forms).

3.3. Carboxylic C–O bands

Typical C–O carboxylic stretching vibrations can be observed in the polymer spectra, at 1222 and 1208 cm^{-1} for poly (4-HMA) and poly (5-HMA), respectively (Figs 2a and 3a). After treatment with calcium solution, these bands are shifted to 1236 and 1215 cm^{-1}, respectively (Figs 2b and 3b). According to the proposed calcium carboxylate structure, and taking into account the FT–IR signals of both polymer-calcium complexes, it is reasonable to consider that there is a partially negative charge distribution over the oxygen atoms and a partially positive one over the calcium atom, as shown in the scheme of Fig. 5. Taking into consideration that the carboxylic C–O bond in this resonance form is now a stronger bond with a semi-double bond character, sharing the electrons of the double bond of the carbonyl oxygen, an increase in wave number of the C–O stretching vibration is consistent with this fact. Salicylic acid shows the same behaviour after treatment with Cl_2Ca, in which the C–O stretch is shifted from 1240 cm^{-1} for pure free acid, to 1250 cm^{-1} after calcium treatment (Fig. 4).

3.4. Thermogravimetric analysis

In order to obtain more information about the complexation process of poly (4-HMA) and poly (5-HMA) with calcium ions, thermograms of both polymers and their corresponding complexes with calcium were recorded dynamically. Fig. 6 shows the thermograms registered for poly (4-HMA) and its calcium salt, together with their corresponding differential diagrams. It is clear from Fig. 6 that the thermal behaviour of poly (4-HMA) is rather different from that of the calcium complex. In both cases, complex curves with several thermodegradative steps are obtained, but the thermogram of the poly (4-HMA)-calcium complex is clearly shifted to lower temperatures, with the appearance of three well-defined minima in the differential curve, instead of only two for the free poly (4-HMA). The poly (4-HMA)–calcium complex gives a stable residue which amounts to 18 wt% of the initial weight of samples analysed, whereas the free polymer presents a total weight loss near to 700 °C, mainly if the

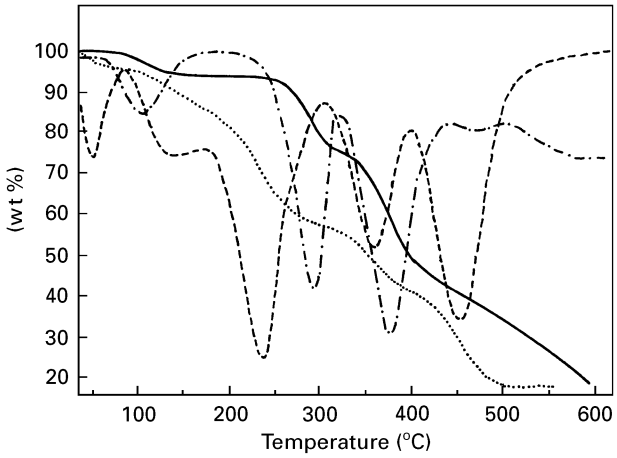

Figure 6 Thermogravimetric diagrams of (—) poly (4-HMA) and (····) poly-4-HMACa and their respective derivate curves: (—·) poly-4-HMA and (––––) poly-4-HMACa.

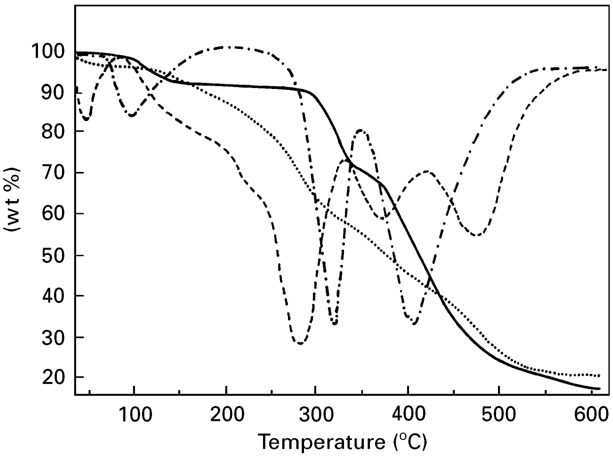

Figure 7 Thermogravimetric diagrams of (—) poly (5-HMA) and (···) poly-5-HMACa and their respective derivate curves; (—·) poly-5-HMA and (–––) poly-5-HMACa.

atmosphere is changed from nitrogen to oxygen to avoid the deposition of carbon residues.

On analysing the shape of the thermograms, it is clear that noticeable differences are observed in the first part of the diagram, corresponding to a temperature interval up to 300 °C. This is clearly explained taking into consideration the ionic interactions of these groups with the calcium ions which are introduced in the polymer chains as ligands between the salicylic groups of neighbouring monomeric units, or even between these groups in different polymeric chains. A loss of water is clearly observed in two steps for the complex poly (4-HMA)–Ca with well-defined minima at 60–70 °C and about 150 °C, which probably correspond to non-bonded water and water bonded to the complexed structures, which presents a relatively restricted diffusion through the stiff, physically cross-linked structure of the complexed polymer–calcium system. Fig. 7 shows the thermograms and the differential diagrams for poly (5-HMA) and the corresponding calcium complex. The results obtained are rather similar to those of the isomeric system, but there are two interesting differences. The first one is a higher calcium residue, which amounts to 20–22 wt%, and the second is the shift of the differential diagram minima of the polymer–calcium complex to higher temperatures (230–240 °C) with respect to that of the poly (4-HMA)–Ca system. This result could indicate a more compact network structure of the poly (5-HMA)–Ca matrix with a higher retention of the water molecules by the interaction with the carboxylic–Ca ionic bonds.

4. Conclusion

High molecular weight polymethacrylamides with salicylic acid side groups form stable ionic complexes with calcium ions, which interact effectively with the hydroxyl –OH and carboxylic –COOH groups of the salicylic side residues to give a physically cross-linked and stiff polymer–calcium matrix.

The relative orientation of the –OH and –COOH groups in isomeric macromolecules of poly (4-HMA)–calcium matrix.

The relative orientation of the –OH and –COOH groups in isomeric macromolecules of poly (4-HMA) and poly (5-HMA) affects the formation of the corresponding complexes with calcium ions, and the analyses by FT–IR and thermogravimetry seem to indicate a more compact structure and higher stiffness of the poly (5-HMA)–Ca in comparison to poly (4-HMA)–Ca complexed matrices.

The results obtained demonstrate that these systems can be used for the preparation of ionomers with the additional properties of the salicylic acid derivatives (analgesic, anti-inflammatory and anti- aggregating effect for platelets). A study of these properties and effects is in progress.

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