Synthesis and Characterization of a New Acrylic Polymeric Ibuprofen Prodrug

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Received 5 October 2009; accepted 10 February 2010
DOI 10.1002/app.32256
Published online 3 May 2010 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Ibuprofen-linked 2-hydroxypropyl acrylate, a new acrylic derivative of ibuprofen in which the drug is separated from the polymerizable double bond by two hydrolytically labile ester bonds, was directly synthesized from the reaction between 2-hydroxypropyl acrylate and ibuprofen. This drug containing monomer was easily homopolymerized by free radical polymerization. The characterization of the resulting products by nuclear magnetic resonance (NMR), size exclusion chromatography (SEC), Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA) indicated that the polymeric prodrugs were successfully synthesized. In addition, the flexible acrylate backbone provides the polymers low-glass transition temperatures and in consequence good processability. Ibuprofen release from the polymer was preliminary evaluated at different pH conditions to show the capacity of these compounds to release the drug under hydrolytic conditions. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 117: 3271–3276, 2010

Key words: ibuprofen; 2-hydroxypropyl acrylate; polymeric prodrug; controlled release

INTRODUCTION

An important advance to increase the therapeutic effectiveness of bioactive agents, while their toxicity decreases, has involved their chemical attachment to macromolecules.[1,2] The preparation of these macromolecular prodrugs, in which active substances are linked to polymeric matrices by means of hydrolyzable covalent bonds, can be carried out by two different approaches. On one hand, it can be done introducing a polymerizable group attached to the drug structure and a posterior polymerization and, on the other hand, it can also be done from the covalent incorporation of the drug into a previously synthesized polymer backbone.[3] In any case and in a general way, the employment of polymeric prodrugs has several advantages over the use of the free form of the drug, as it was explained by Babazadeh.[4] Therefore, the polymeric prodrug conjugates have led into a new era of polymeric drug delivery systems.[5–8]

2-Arylpropionic acids (profens) are an important class of nonsteroidal anti-inflammatory drugs (NSAIDs).[9,10] Nevertheless, pharmacological studies of profens have indicated that apart from their frequent poor water solubility,[11] gastrointestinal side effects, are their worst disadvantage.[12] In addition, their therapeutic uses are often restricted by the necessity to deliver the drug to specific sites of target organ or tissue. These problems can be solved by the preparation of polymeric prodrug backbones via hydrolyzable bonds and, for this reason, some NSAIDs such as ibuprofen,[13–16] indomethacin,[15,17] ketoprofen,[14] and diclofenac[18] have been chemically attached to various polymer backbones and their hydrolytic behavior studied. Therefore, this kind of polymeric prodrugs can be useful for localized and prolonged duration of drug action by parental administration[19] or as dermal prodrugs.[20]

According to these facts, the main aim of this article is to synthesize new acrylic polymeric prodrugs from the free radical polymerization of a new acrylic monomer with an ibuprofen pendant group (ibuprofen-linked 2-hydroxypropyl acrylate, ILHPA), as it is shown in Scheme 1. The synthetic procedure used in this contribution has the advantages that the acrylic ibuprofen monomer, which incorporates a spacer group, can be obtained in high yield by one-step reaction and it can be further polymerized by free radical polymerization. Moreover, the obtained polymeric prodrugs have a flexible acrylic backbone and as a result, they should exhibit low-glass transition temperatures (T_g) and a relatively low viscosity,

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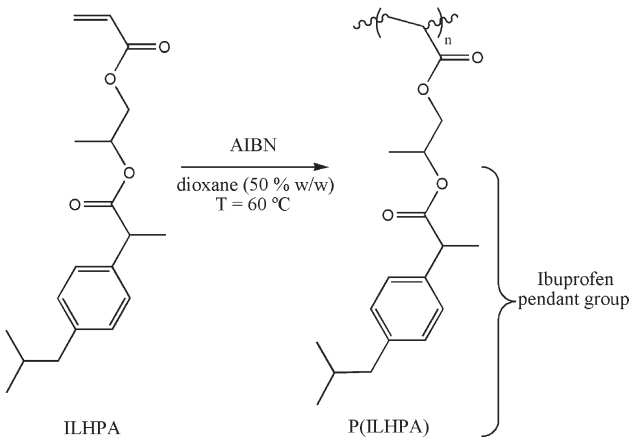
Contract grant sponsor: Ministerio de Ciencia e Innovación (for a Juan de la Cierva contract); contract grant number: CTQ 2008-03229.
Contract grant sponsor: Comunidad Autónoma de Madrid; contract grant number: CAM S0505/MAT/0227.
Contract grant sponsor: Ministerio de Sanidad y Consumo; contract grant number: FIS- PI081677.
Contract grant sponsor: CSIC (for a JAE-PRE grant).



Scheme 1 Chemical structure of ILHPA and its polymerization process.

properties that are interesting for technological applications. Furthermore, they could release an ibuprofen molecule from each monomeric unit by the hydrolysis of the ester group. For this reason, some drug release experiments were also performed to check if the ester bond breaking occurs under neutral and basic conditions, although the central objectives of the present work are the study of the ibuprofen-acrylic monomer synthesis, its polymerization process, and also the complete characterization of the synthesized polymers by nuclear magnetic resonance (NMR), Fourier transform infrared (FTIR) spectroscopy, size exclusion chromatography (SEC), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA).

EXPERIMENTAL

Materials

N,N′-dicyclohexylcarbodiimide (DCC, Aldrich 99%), 4-(dimethylamino)pyridine (DMAP, Aldrich 99%), 2-hydroxypropyl acrylate (HPA, BASF), sodium bicarbonate (Quimicen, 99.9%), hydrochloric acid (Panreac 37%), sodium chloride (Panreac 99.5%), and magnesium sulfate anhydrous (Aldrich, 99.9%) were employed as received. Azobisisobutyronitrile (AIBN, Aldrich) was recrystallized from methanol, whereas ibuprofen (Aldrich, 98%) from an acetone/hexane mixture (1/1 v/v). Solvents *n*-hexane (Panreac 98%), dichloromethane (CH_2Cl_2, Fluka 99.9%), dioxane (Panreac 99%), acetone (Normapur, 99.8%), chloroform (Sds, 99.9%), methanol (Fluka 99.8%) and *N,N′*-dimethyl formamide (DMF, Scharlau 99%) were employed without previous purification. Water for hydrolysis reactions was Milli.Q from water purification facility (millipore Milli-U10). The basic solution at pH 12 was prepared with sodium hydroxide (Panreac 98%) and the phosphate buffer solution (PBS) at pH 7 was prepared employing sodium dihydrogen phosphate anhydrous (Fluka 99%), disodium hydrogen phosphate (Panreac 98%), and sodium chloride to keep constant the ionic strength (0.1*M*).

Synthesis of ibuprofen-linked 2-hydroxypropyl acrylate

A solution of DCC (29.1 mmol) in 40 mL of CH_2Cl_2 was added dropwise at 0°C to a solution of ibuprofen (29.1 mmol) and DMAP (14.55 mmol) dissolved in 40 mL of CH_2Cl_2. Keeping the temperature, a solution of HPA (24.25 mmol) in others 40 mL of CH_2Cl_2 was added dropwise. After that, the reaction mixture was warmed to room temperature and the reaction continued 24 h. Thus, the precipitate was filtered and the organic layer was sequentially extracted three times by 10 wt % of $NaHCO_3$, twice by HCl (2*N*), once by deionised water, and finally by a saturated NaCl solution. The extracted organic solution was dried over $MgSO_4$ anhydrous and the solvent was removed under vacuum. A yellow liquid was obtained. After set aside at room temperature overnight, a white precipitate appeared. It was removed and the final yellowish liquid was obtained in a yield of 86%. Analyses: calculated for $C_{19}O_4H_{26}$ (%): C, 71.65; H, 8.23; O, 20.12; found C, 71.98; H, 8.35; O, 19.67. FTIR (KBr, cm^{-1}): 3100, 3070, 3040 (=C—H); 2900, 2890 (C—H aliphatic); 1740, 1720 (C=O); 1660, 1645, 1625 (C=C); 1200, 1170 (C—O). ^{1}H-NMR ($CDCl_3$, δ ppm): 7.02 (q, 4H, CH aromatic), 6.20 (m, 1H, =C$\boldsymbol{H}_2$ cis), 5.93 (m, 1H, =CH(CO)), 5.69 (m, 1H, =C$\boldsymbol{H}_2$ trans), 5.06 (m, 1H, ∼O—C$\boldsymbol{H}$(CH_3)—O∼), 4.03 (m, 2H, ∼O—C$\boldsymbol{H}_2$∼), 3.59 (q, 1H, ∼C$\boldsymbol{H}$(CH_3)—CO∼), 2.33 (d, 2H, ∼C$\boldsymbol{H}_2$—CH(CH_3)$_2$), 1.73 (m, 1H, ∼CH_2—C$\boldsymbol{H}$(CH_3)$_2$), 1.37 (d, 3H, ∼CH(C$\boldsymbol{H}_3$)—CO∼), 1.06 (m, 3H, ∼O—CH(C$\boldsymbol{H}_3$)—O∼), 0.78 (d, 6H, ∼CH_2—CH(C$\boldsymbol{H}_3$)$_2$). ^{13}C-NMR ($CDCl_3$, δ ppm): 173 (∼Ar—CH(CH_3) $\boldsymbol{C}$O—O∼), 164 (CH_2=CH—$\boldsymbol{C}$O—O∼), 139 ($\boldsymbol{C}H_{Ar}$—CH_2—CH(CH_3)$_2$), 135 ($\boldsymbol{C}H_{Ar}$—CH(CH_3)—CO—O∼), 126–129 (6C Ar), 67 (∼O—$\boldsymbol{C}H_2$—CH(CH_3)—O∼), 65 (∼O—CH_2—$\boldsymbol{C}$H(CH_3)—O∼), 44 (∼Ar—$\boldsymbol{C}H_2$—CH(CH_3)$_2$), 29 (∼Ar—$\boldsymbol{C}$H(CH_3)CO—O∼), 24 (∼Ar—CH_2—$\boldsymbol{C}$H(CH_3)$_2$), 21 (2C ∼Ar—CH_2—CH($\boldsymbol{C}H_3$)$_2$), 17 (∼O—CH_2—CH($\boldsymbol{C}H_3$)—O∼) and 15 (∼Ar—CH($\boldsymbol{C}H_3$)CO—O∼). MS (API-ES pos) *m/z* [M+Na^+] = 341.5. UV–Visible (dioxane, 25°C): λ_{max} = 233.5 nm.

Free radical polymerization of ILHPA: General procedure

The polymerization of ILHPA was carried out in dioxane solution (50% w/w) at 60°C employing AIBN as initiator. These conditions were chosen in base of the work of Davaran et al.[3] All experiments were carried out in Pyrex glass ampoules sealed off

TABLE I
Preparation Conditions and Characterization Parameters of the Different P(ILHPA) Homopolymers Synthesized in Dioxane Solution (50% w/w, $[ILHPA]_0$ = 4.73 mmol) at 60°C with AIBN as Initiator

Sample	$[AIBN]_0$ (% mol)	Time (h)	Conver.[a] (%)	$M_{n,SEC}$[b] (g mol^{-1})	M_w/M_n[b]	T_g[c] (K)	ΔC_p[c] (J K^{-1} g^{-1})	T_{max}[d] (K)
1	3.87	6	68	20753	2.84	274.8	0.29	645.3
2	3.87	4	64	15350	2.16	276.8	0.27	642.9
3	3.87	2	59	7793	1.29	276.0	0.33	642.8
4	4.53	4	71	12031	1.88	277.7	0.34	640.6
5	5.18	4	73	10479	2.01	276.6	0.31	642.0

[a] Determined gravimetrically.
[b] By SEC.
[c] By DSC.
[d] By TGA.

under dried nitrogen in a thermostatic bath. After the desired time, the mixture was poured into a large amount of cold methanol as nonsolvent. The precipitated polymer (noncolored, viscous, and chloroform soluble), P(ILHPA), was collected and dried in vacuum. Additional polymerization conditions are collected in Table I.

Method of hydrolysis of P(ILHPA): Ibuprofen release

Dried polymers (~ 20 mg) were dissolved in 1 mL of chloroform. These solutions were put in the bottom of a flat vial (Ø = 22 mm) and then, the polymers were dried at room temperature during 48 h. Afterward, 20 mL of pH-controlled aqueous solution and a magnetic stir were added to each sample and the vials were sealed off. Then, the vials were put inside a thermostatic bath at 37°C and the hydrolytic solution was stirred. After the desire times, the ibuprofen release was evaluated by measuring the absorbance at 264 nm with a UV–Visible spectrophotometer (Cary 3 BIO-Varian) and employing a previous ibuprofen calibration at 37°C in a PBS at pH 7 (molar extinction coefficient, $\varepsilon_{264} = 350.6 \pm 8.7$ cm^{-1} mol^{-1} L). The characterization of the hydrolysis products by mass spectroscopy and ^{1}H-NMR (D_2O) determined the ibuprofen formation, in the same way that it was previously observed by Babazadeh with others ibuprofen prodrugs.[13–16]

Characterization

Infrared spectra were recorded by use of KBr pellets on a PerkinElmer Spectrum One FTIR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ or D_2O at room temperature using the typical acquisition parameters. Elemental analysis was carried out using a Leco CHNS-932. Mass spectroscopy was realized in a LC MS 1100. Molecular weight (M_n) and molecular weight distribution (MWD) of polymers were determined by SEC with a Water Series 410 instrument (mobile phase: DMF with LiBr (0.1 wt %) at 1 mL/min and 50°C). Poly(methyl methacrylate) [P(MMA)] standards, between 2.99 × 10^3 and 4.8 × 10^5 g mol^{-1}, were employed for the SEC calibration. The glass transition temperatures (T_g)s were measured by means of DSC using a PerkinElmer DSC 7 with air liquid for low temperatures (samples were scanned at 10 K min^{-1} under 20 mL min^{-1} of dry nitrogen). T_g values were estimated as it was previously described,[21] while the specific heat increment (ΔC_p) values were calculated from the vertical distance between the two extrapolated baselines in the second run. In addition, the thermal stability of the polymers was determined from thermogravimetric analysis with a TA TGAQ500 (10 K min^{-1} under 20 mL min^{-1} of dry nitrogen). The temperature at which the weight loss rate is maximum (T_{max}) was determined from the maximum of the peak of the first derivative of the weight lost.

RESULTS AND DISCUSSION

Synthesis and characterization of the polymeric prodrugs of P(ILHPA)

The synthetic methodology of the incorporation of ibuprofen units into a polymerizable group to form polymeric prodrugs in a posterior step, is not something new. Thus, Babazadeh[16] and Chang et al.[14] synthesized methacrylic monomers based on ibuprofen. Moreover, Davaran et al.[3] studied the influence of the spacer groups in acrylic and methacrylic monomers synthesized from two synthetic steps. Whereas, Cai et al.[10] carried out the preparation of vinyl monomers also employing various reaction steps.

The synthetic procedure employed in this work presents some advantages. The monomer ILHPA has been obtained following the reaction described by Gnanou and Rempp[22] employing directly 2-hydroxypropyl acrylate and ibuprofen. The novelty

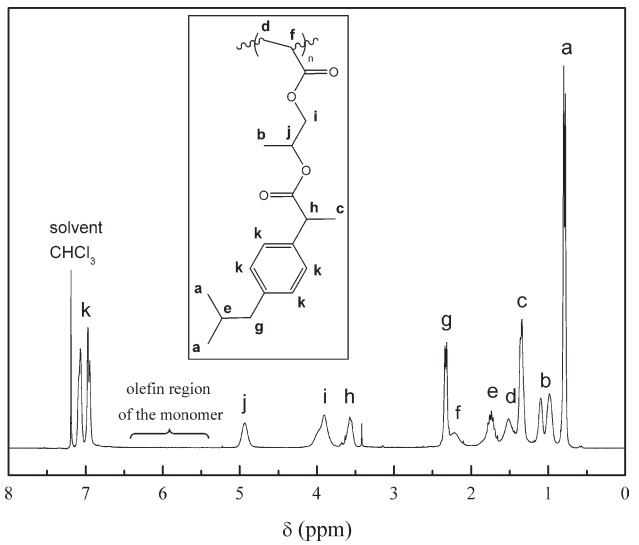


Figure 1 ^{1}H-NMR spectrum in $CDCl_3$ of a P(ILHPA) homopolymer (sample 1) synthesized by free radical polymerization.

of this synthesis is that, in just one step, the hydrolyzable-ibuprofen pendant group acrylic monomer is obtained with very high yield comparing with other similar systems.[3,4,10,14,16] Therefore, the presence of an ibuprofen group bound to the rest of the molecule by hydrolyzable ester groups will lead to the formation of bioactive ibuprofen molecules by the hydrolysis of these ester groups. Moreover, the presence of the spacer group favors these hydrolysis reactions[3] and also, introduces a new hydrolyzable-broken point. In addition, the fact that the polymerizable group is acrylic establishes that the polymers formed should show low-glass transition temperatures (T_g) and therefore, they will be malleable at room temperature.

Drug containing monomer, ILHPA, was easily homopolymerized several times by free radical polymerization under the conditions described previously in the experimental section. Two main experimental variables were studied in the homopolymerization of ILHPA: reaction time and feed molar ratio of initiator. In all cases, ^{1}H-NMR and FTIR confirmed the formation of the desired polymer, P(ILHPA). As an example, Figures 1 and 2 show the NMR spectrum and the FTIR spectrum, respectively, of the P(ILHPA) called sample 1 with the corresponding signal assignment. Comparing with the monomer ^{1}H-NMR signals given in the experimental section, those signals corresponding to the acrylic double bond are missing while those of the aliphatic main chain appear. Consequently and taking into account the rest of signals, the projected polymer structure was confirmed in all cases. In the FTIR spectrum, those absorptions due to the double bond of the monomer also disappear. Coming back to Table I, it is observed that as higher is the polymerization time, higher conversions are achieved, as it was expected. These conversions were determined gravimetrically from the weight of the dried polymer and the weight of the monomer employed in the feed. In addition, the number average molecular weight determined by SEC ($M_{n,SEC}$) increases when the conversion does for the same concentration of initiator. This increase in molecular masses could be consequence of a transfer process within the growing polymer chains. This hypothesis is supported by the values of the polydispersity indexes (M_w/M_n), which also increase with an increase of the monomer conversion. On the other hand, an increase in the monomer/initiator feed ratio establishes the formation of polymers with lower conversions but with higher molecular weights. At this point, it is relevant to mention that these molecular weights are determined by SEC and therefore, they are not absolute values since they depend on the experimental SEC conditions and on the P(MMA)s standards employed in the calibration.

Thermal properties of the polymeric prodrugs of P(ILHPA)

The thermal properties of the new acrylic polymeric prodrugs of P(ILHPA) were studied by DSC and TGA to complete their characterization. As a representative example, Figure 3 shows the different thermograms obtained with the polymer called sample 2. However, the characterization parameters determined from these studies for all samples are included in Table I.

From DSC analysis T_g values were determined and therefore, the initial hypothesis that these acrylic homopolymers show a T_g bellow room temperature

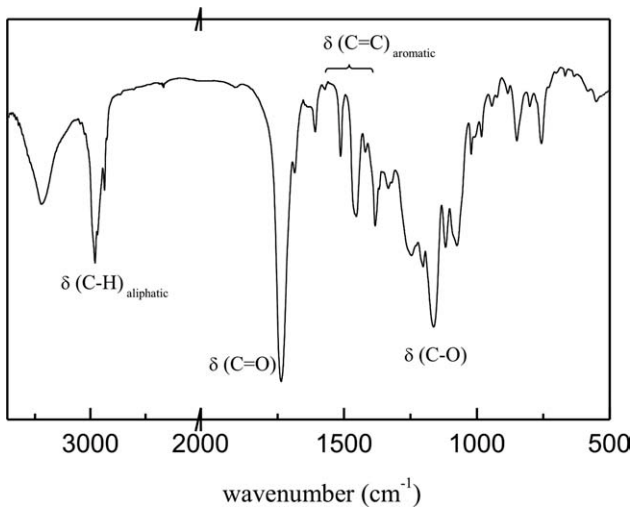


Figure 2 FTIR spectrum in KBr of a P(ILHPA) homopolymer (sample 1) synthesized by free radical polymerization.

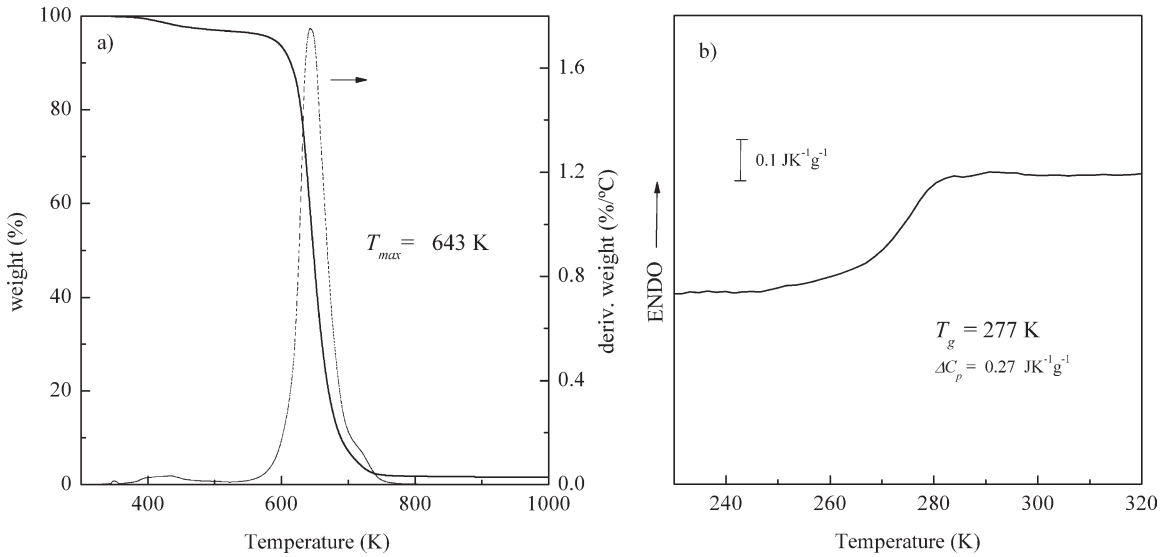


Figure 3 (a) TGA curve and its derivative and (b) DSC curve of a P(ILHPA) homopolymer (sample 2) synthesized by free radical polymerization.

was confirmed. Values between 274 and 278 K were obtained for the different P(ILHPA)s. No coherent variation of these values with the molecular weight is observed at the range under study. Then, we assume that the determined T_gs do not depend on the molecular weight for this molecular weight range and therefore, the average T_g value can be calculated, obtaining that $T_{g,\mathrm{P(ILHPA)}} = 276.4 \pm 1.1$ K. Comparing with other acrylic homopolymers, for instance poly(propyl acrylate) (236 K),[23] this value is quite high, which is attributed to the rigid ibuprofen pendant groups that decrease the mobility of the chains. However, if this value is compared with those values described previously for other ibuprofen prodrugs,[3,14] it can be observed that it is much lower, which means that these polymers should show better processing properties. On the other hand, the ΔC_p values are similar for all samples, as it corresponds to the analysis of the same type of homopolymers, $\Delta C_{g,\mathrm{P(ILHPA)}} = 0.31 \pm 0.03$ J K^{-1} g^{-1}.

From TGA, it was possible to determine that the samples showed three main decomposition processes at: ~424 K, ~639 K, and ~721 K. The main decomposition was the second one, where more than the 90% of the weight of the samples is lost. From the maximum of the peak of the derivate curve of this process, the $T_{\mathrm{max.}}$ for each sample could be determined. These values are also included in Table I. Newly, the samples show similar results and therefore, an average value could be calculated: $T_{\mathrm{max,P(ILHPA)}} = 642.7 \pm 1.7$ K. This value is in agreement with the results found for other acrylic polymers incorporating voluminous (aromatic rings) pendant groups.[24,25] It is worthy to mention, at this point, that TGA results are not directly relevant for biomedical applications. However, we consider that determination of thermal stability is necessary to complete the characterization of these compounds. On the other hand, the decomposition temperature is related to the degradation time at room temperature and therefore, they can be important to know the lifetime of these polymeric prodrugs.

Drug release by hydrolysis of the polymeric prodrugs of P(ILHPA)

Each monomeric unit of the acrylic polymers synthesized presents an ibuprofen pendant group linked

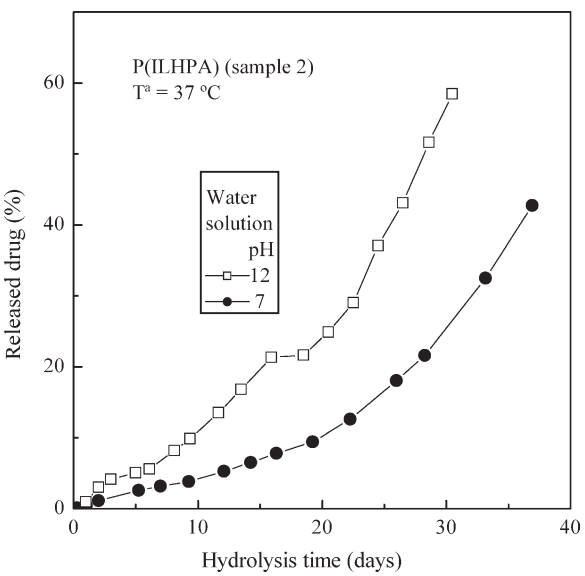


Figure 4 Percentage of released ibuprofen from P(ILHPA) homopolymer (sample 2) as a function of time at 37°C for different pH conditions.

by hydrolyzable groups, as it was shown in scheme 1. Therefore, these polymers should release ibuprofen under hydrolysis conditions. To show this relevant characteristic, some preliminary qualitative degradation studies at different pH solutions were carried out employing the sample 2, according with the procedure described by Babazadeh.[16] This author also established that this kind of ibuprofen monomers have a hydrolysis rate higher as higher is the pH.[4] In fact, at acid pH the ibuprofen release took place very slowly. For this reason, the hydrolysis study was made at pH 7 and at pH 12 (very alkaline medium).

The kinetic rates of ibuprofen release at these pH conditions, followed by UV–Vis spectroscopy, are shown in Figure 4. The degradation process is very slow, if it is compared with the degradation rates of similar polymeric prodrugs.[3,14,16] This fact is due to the hydrophobic character of the P(ILHPA) homopolymer, which determines that it is not soluble in water solutions, and also because the low area of the polymer exposed to the hydrolysis solution. Other interesting result observed in Figure 4 is that the percentage of ibuprofen released increases exponentially with time. That means that the hydrolysis rate increases as higher is the percentage of drug released. This effect can be attributed to an increase of the polymer hydrophilicity as the ester linkages break and lead to either an acid or alcohol functionality. Consequently, this experimental evidence supports the hypotheses that the copolymerization of this monomer with hydrophilic comonomers would produce polymers with higher hydrolysis rate, as it was previously observed by other author.[3,14,16] Another comment from Figure 4 is that under alkaline pH the ibuprofen is faster released than under neutral conditions, which is attributed to the logical higher hydrolization rate of the ester groups in this environment. At this point, it is important to mention that in this work it just wanted to show that the synthesized polymers have the property of release ibuprofen under hydrolytic conditions. In a further study, copolymerization with hydrophilic monomers will be attempt for the optimization of the degradation rate.

CONCLUSIONS

A new acrylic monomer with an ibuprofen pendant group has been synthesized in a one-step process. This monomer has been polymerized by free radical polymerization, obtaining well-structured homopolymers with conversions and molecular weights that depend on the experimental conditions. The polymers show a $T_{max,\ P(ILHPA)} = 642.7 \pm 1.7$ K and $T_{g,P(ILHPA)} = 276.4 \pm 1.1$ K ($\Delta C_{g,P(ILHPA)} = 0.31 \pm 0.03$ J K^{-1} g^{-1}), which are expected values. These homopolymers show the ability to release ibuprofen under hydrolysis conditions, although the hydrolysis rate will have to be optimized in the future though copolymerization with hydrophilic monomers for a possible application in drug delivery.

The authors are very gratefull to Dr. Marta Fernández for her assistance in the SEC measurements.

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