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Monitoring ibuprofen enantiomers released from polymeric systems

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Abstract

Two methacrylic derivatives of ibuprofen (*N*-{4-[2-(4-isobutylphenyl)propionyloxy]phenyl} methacrylamide (MAI) and 2-[(4-isobutylphenyl)propionyloxy]ethyl methacrylate (MEI)) were used together with 2-hydroxyethyl methacrylate (HEMA) to synthesize four polymeric materials: two hydrophobic homopolymers, PMAI and PMEI, and two hydrophilic copolymers containing 70% (w/w) HEMA, MAI–HEMA 30 and MEI–HEMA 30. The enantiomeric determination of *R*- and *S*-IBU released from these four systems has been carried out by capillary electrophoresis. Release of *R*- and *S*-IBU was monitored during in vitro assays done at 37 °C at pH 7.4 and 10 in buffered solutions and rat plasma. There is a hydrolytical activation in plasma and at pH 10 compared to pH 7.4; moreover, the release rate from the copolymers is much higher than from the homopolymers as a consequence of the greater hydrophilic character. A slight excess of the *S*-enantiomer of IBU is observed in all the experiments, being more relevant at higher release rates, i.e. copolymers at pH 10. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Controlled release; Polymeric drug; Ibuprofen enantiomers; Chiral separation; Capillary electrophoresis

1. Introduction

Ibuprofen (IBU) belongs to the arylpropionic acids family, which is a class of non-steroidal anti-inflammatory drugs, NSAIDs, widely used in the treatment of arthropathies because of their potent anti-inflammatory and analgesic activity. An ibuprofen controlled release system would be useful especially in chronic diseases such as rheumatoid arthritis. In this sense, there are several examples in the literature of drug delivery systems bearing ibuprofen chemically linked to a macromolecular backbone (Cecchi et al., 1981; Chang et al., 1988; Larsen and Johansen, 1989; Davaran and Entezami, 1997, 1998; Parejo et al., 1998, 2000; Gallardo et al., 2001). However, no attention has been devoted to the possible enantioselectivity of *R*- and *S*-IBU release, despite its relevance. Although their activity resides in the *S*-enantiomers (the *R* being inactive), most of the times the drug is used as a racemate. The unidirectional bioinversion of *R*- to *S*-IBU occurring in vivo (Knihinicki et al., 1989), supports in some way the commercial use of the racemate. Moreover, recent investigations have also indicated that the *R*-enantiomers of these agents may not be totally devoid of useful biological activity, that the formation of acyl-CoA derivatives results in interactions with lipid biochemistry, and has provided new insights into the disposition of these drugs in man (Tan et al., 1999). Ibuprofen represents a classical example of a drug where stereochemical considerations are essential for an understanding of its biological properties. Attending to this relevance, enantiospecific analytical methodologies suitable for the determination of both the drug and its metabolites is essential in order to evaluate the significance of stereoselectivity both in terms of drug action and disposition. In this work the enantiomeric monitoring of the ibuprofen release from different polymeric drugs and for several in vitro experiments is described using capillary electrophoresis (CE).

CE has been shown to be a powerful analytical tool for the separation of chiral compounds (Chankvetadze, 1997). CE provides well-resolved and efficient separations of enantiomers in short analysis times (usually shorter than 30 min). Moreover, the low consumption of enantioselective

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reagents makes this technique especially suitable for chiral separations, where frequently very expensive compounds have to be used.

2. Materials and methods

2.1. Chemicals

N-{4-[2-(4-isobutylphenyl)propionyloxy]phenyl} methacrylamide (MAI) and 2-[(4-isobutylphenyl)propionyloxy]ethyl methacrylate (MEI), were prepared as described elsewhere (Gallardo and San Román, 1993a; Parejo et al., 1998; for structures, see Fig. 1). 2-Hydroxyethyl methacrylate (HEMA) was purified according to the literature (Fort and Polyzoidis, 1976). *N*,*N*-Dimethylformamide (DMF) was dried over anhydrous magnesium sulphate for 2 days and later with phosphoric anhydride overnight. After drying, DMF was distilled under reduced pressure of nitrogen. 2,2′-Azobisisobutyronitrile was purified by fractional crystallization from methanol (m.p. = 104 °C).

All other chemicals were of analytical reagent grade and used as received. Dextrin 10, boric acid and sodium tetraborate hydrate from Aldrich (Milwaukee, WI) were used for the CE running buffers at the concentrations and pHs indicated. The buffers were stored at 4 °C and warmed at room temperature before being used. Acetonitrile, sodium dodecyl sulfate (SDS) and sodium hydroxide were from Merck (Darmstadt, Germany). Distilled water was deionized using a Milli-Q system (Millipore, Bedford, MA).

2.2. Polymerization

The monomers were polymerized or copolymerized at 50 °C in a thermostatic bath regulated with a precision of ±0.1 °C, using 2,2′-azobisisobutyronitrile as initiator ($[I] = 1.5 \times 10^{-2}$ mol/l) and dimethylformamide as solvent ([M] = 1 mol/l) (M = monomer). The reactions were carried out in Pyrex glass ampoules over 5 h in nitrogen atmosphere. The polymer was isolated by pouring the reaction mixture into a large excess of diethylether or methanol. The precipitated samples were filtered off, washed with the corresponding non-solvent and dried at reduced pressure to constant weight.

Average composition of the prepared systems was analysed by ^{1}H and ^{13}C NMR spectroscopy. Molecular weight and molecular weight distribution were determined by size exclusion chromatography. Experimental details are reported elsewhere (Parejo et al., 2000).

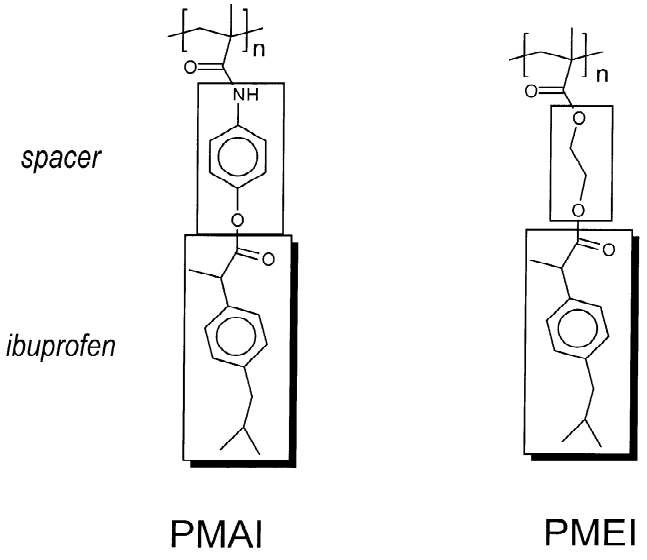

Fig. 1. Chemical structure of the active units MAI and MEI in the homopolymers.

2.3. Obtaining plasma

Blood from ether anaesthetized male Wistar rats weighing 250–300 g was collected by cardiac puncture and mixed with a 3.1% citrate solution as anticoagulant (10:1 ratio). Plasma was separated by centrifugation of blood at 3000 rev./min at room temperature and used immediately.

2.4. Swelling experiments

Films with an average thickness of 0.5 mm were prepared by casting from solutions of the polymers in dimethylformamide using teflon moulds. Films were finally vacuum dried and cut into discs of about 1 cm diameter. These fragments were placed into a flask with 10 ml buffer solution of pH 7.4 (20 mM phosphate) and kept in a thermostated bath at 37 °C. The water uptake, *W*, was calculated by measuring the weight gain of the sample at different times after carefully wiping the surface with a filter paper, using the following equation:

$$W = (M - M_0) \times 100/M_0$$

where M_0 is the weight of the dry sample and M is that of the sample at time t.

2.5. In vitro release experiment

Pieces of ~0.2 cm^2 of copolymer films were engaged in a polyester mesh and immersed in 1 ml of buffered solutions (20 mM phosphate at pH 7.4 or 20 mM sodium tetraborate at pH 10, containing 2% of Tween) or plasma and incubated in triplicate at 37 °C in a thermostated oven or in an Infors incubator shaker UNITRON, respectively. In the case of the homopolymers, fine powder was used instead of films and the procedure was similar for both cases. Fifty μl of the buffer or plasma were collected at appropriate times and replaced by fresh medium. The collected samples (50 μl) from plasma experiments were precipitated with 100 μl of acetonitrile, centrifuged at

15,000 rev./min for 10 min and the supernatant was collected for CE analysis. The recovery of this procedure was the same for both IBU enantiomers and equal to 103% ($\%RSD_{n=4} = 10.4\%$). All the samples were injected in triplicate in CE. The dilution caused by adding new buffer was corrected. These measurements were used to determine the enantiomeric excess as the *S*-IBU/*R*-IBU ratio.

2.6. CE conditions

The analyses were carried out in a P/ACE 2050 (Beckman Instruments, Fullerton, CA, USA) CE apparatus, equipped with a UV–Vis detector working at 200 nm. Bare fused-silica capillaries with 50 μm I.D. were purchased from Composite Metal Services (Worcester, UK). Injections were made at the anodic end using N_2 pressure of 0.5 p.s.i. for a given time (1 p.s.i. = 6894.76 Pa). The instrument was controlled by a Compact Deskpro PC running the System GOLD software from Beckman.

Before first use, a new capillary was preconditioned by rinsing with 0.1 M NaOH for 30 min. At the start of each day, the capillary was conditioned by carrying out three consecutive separations of a standard dissolution containing racemic IBU. Between injections, the capillary was rinsed using 0.1 M NaOH (containing 50 mM SDS) and water, both for 1 min, and running buffer for 2 min. At the end of the day, the capillary was rinsed with deionized water for 5 min and stored overnight with water inside.

3. Results and discussion

3.1. CE monitoring of R- and S-IBU released from polymeric devices

The chemical structures of the precursor monomers bearing IBU used to synthesize the polymeric devices are represented in Fig. 1. The synthesis and characterization of copolymers of these two methacrylic compounds with hydroxyethyl methacrylate, HEMA, and the average release of the NSAIDs components in buffered solution, have been described in earlier articles (Parejo et al., 1998; Gallardo et al., 2001). The present work is devoted to the study of the release behavior in different conditions, using enzymatic activity associated to plasma, and to the analysis of the possible enantioselectivity of the ibuprofen release from polymeric drugs fabricated using the structures of Fig. 1 (and taking the homopolymers as reference samples). Basically, we have prepared by radical polymerization two types of systems: (a) two homopolymers, poly-MAI and poly-MEI and (b) two hydrophilic copolymers by copolymerization with HEMA. We have performed a complete in vitro release study using different conditions (pHs 7.4 and 10, or rat plasma as simple enzymatic model) and we have analyzed the release of the *R*- and *S*-IBU forms by using a new capillary electrophoresis method (CE). The optimized analytical method consists of a cheap, fast and sensitive protocol that allows separation of *R*- and *S*-IBU enantiomers in less than 5 min, with efficiencies higher than 300,000 plates/m for both compounds. Besides, the sensitivity of this method was good (i.e. LOD of 0.001 mg/ml) as well as its reproducibility (Simó et al., 2002). The method uses a sodium tetraborate buffer at pH 9 containing 6% of Dextrin 10, and the separations are done in a bare fused silica of 37 cm of total length with 50 μm I.D. Besides, as expected, the injection of equal concentrations of *R*- and *S*-IBU enantiomers provided similar corrected peak areas (i.e. peak area/migration time) for both enantiomers. For instance, concentrations of 0.005 mg/ml of *R*- and *S*-IBU injected in the CE system provided corrected peak areas equal to 0.0105 and 0.0104 respectively, while concentrations of 0.17 mg/ml provided a corrected peak area of 0.378 for *R*-IBU and 0.382 for *S*-IBU. Using this CE method, separations of *R*- and *S*-IBU such as the ones shown in Figs. 2 and 3 were typically obtained. Fig. 2 shows the release of IBU forms obtained at three different times from the homopolymers poly-MAI and poly-MEI during the in vitro experiments done at pH 10. Fig. 3 shows the different release of *R*- and *S*-IBU from the copolymer MAI–HEMA obtained at three different times during in vitro experiments done at pH 7.4

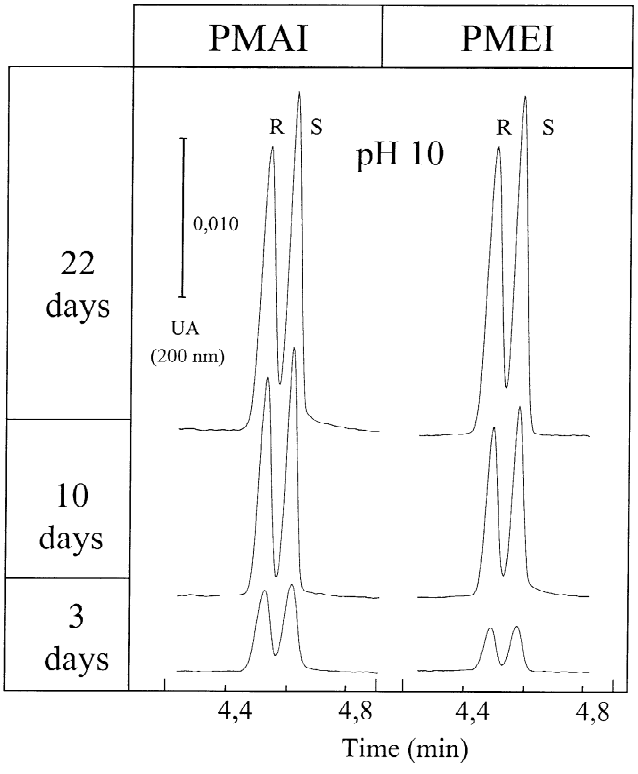

Fig. 2. Electropherograms of *R*- and *S*-IBU forms released from MAI and MEI homopolymers during in vitro assays at pH 10. Separation conditions, bare silica capillary with 30 cm effective length and 37 cm total length (50 μm i.d.). Separation voltage, +20 kV, detection at 200 nm. Injection at 0.5 p.s.i. for 3 s. Running buffer, 150 mM borate at pH 9 with 6% Dextrin 10 (w/v). Separation temperature, 20 °C.

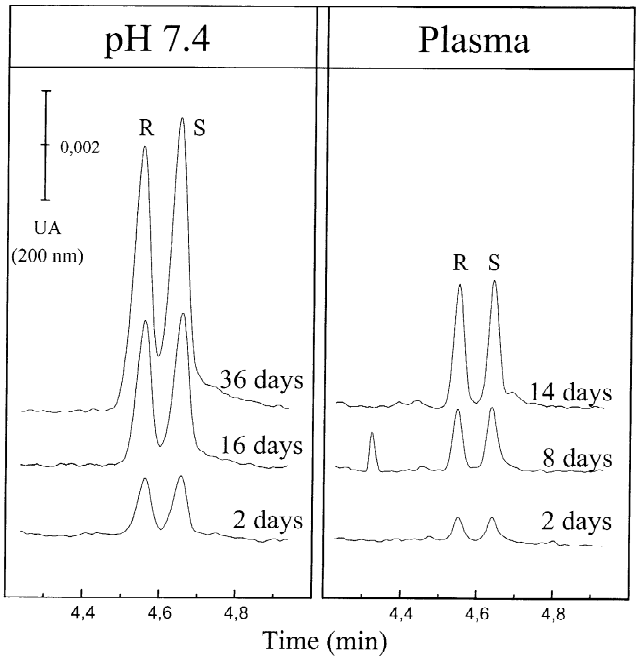

Fig. 3. Separation of *R*- and *S*-IBU forms released from MAI–HIBU copolymer during in vitro assays at two different media (pH 7.4 and plasma). Separation conditions, bare silica capillary with 30 cm effective length and 37 cm total length (50 μm i.d.). Separation voltage, +20 kV, detection at 200 nm. Injection at 0.5 p.s.i. for 3 s. Running buffer, 150 mM borate at pH 9 with 6% Dextrin 10 (w/v). Separation temperature, 20 °C.

and rat plasma (note that samples from plasma are diluted threefold prior to their injection in the CE apparatus). The different release rate of IBU is due to both the different nature of the polymeric device (i.e. homopolymer vs. copolymer) and the different media used to carry out the in vitro assays as discussed in the next section.

3.2. Polymeric device description

Although we have not performed a direct analysis of the chirality of the ibuprofen residues in the polymeric chains (which is a difficult task), the enantiomer ratio must be 1:1 since the ratio of the starting ibuprofen molecules is 1:1, the reactivity of this carboxylic acid (ibuprofen) in esterification reactions does not depend on the chirality (therefore the enantiomer ratio of the monomers must be 1:1) and the polymerization is carried out till 100% conversion. It has been demonstrated widely that the free radical polymerization is not sensitive to the chirality of enantioisomers and logically it can be expected that there is not any change of the average enantiomeric composition during the polymerization process.

In addition to the dissimilar hydrolytical reactivity of the two esters (the aromatic ester of MAI being more reactive than the aliphatic ester of MEI) (Gallardo et al., 2001), there is a great difference between the two types of devices (homo and copolymers), as can be seen from Table 1 and Fig. 5 where MAI polymers have been represented as examples. The repeating units in these polymer chains have a quaternary carbon that can be considered as a pseudoasymmetric centre, sensitive to the stereochemical configuration of their corresponding side substituents, i.e. αCH_3 and carboxylic ester or amide functions. We have found that the stereochemical distribution of the side group of acrylic monomers in free radical copolymerization in general follows Bernoullian statistics (San Román and Valero, 1990; San Román and Levenfeld, 1990). On this basis, we assume that the configurational sequence distribution may be described according to Bernoullian statistics with the isotacticity parameter σ, where σ is the probability of generating a meso dyad (m) between an ending growing radical and incoming monomer (and $1-\sigma$ being the probability of generating a racemic dyad, r) (Bovey, 1982). This parameter can be determined from the analysis of the stereochemical distribution derived from NMR data. As is shown in Fig. 4, the α-methyl or C=O (for the PMAI and PMEI, respectively) signals in the ^{1}H and ^{13}C-NMR spectra, respectively, split in several signals, which can be tentatively assigned to triads and pentads as is shown in the figure, according to analysis of sequences for similar polymers (Gallardo and San Román, 1994). From this assignment, we have calculated the isotacticity parameter σ that gave a better fitting of the data according to a Bernoullian statistic, obtaining as best isotacticity parameters (see Table 1), $\sigma = 0.17$ (PMAI) and $\sigma = 0.20$ (PMEI). As a conclusion of this analysis, the homopolymers are highly syndiotactic as other similar polymethacrylates or poly-methacrylamides (Gallardo and San

Table 1
Some characteristics of the four polymeric systems used in this work

	f(HEMA)[a]	σ[b]	F(HMH)[c]	F(MMM)[c]	M_n[d]	Swelling D[e]
PMAI	0	0.17	0	1	46000	<2
PMEI	0	0.20	0	1	41000	<2
MAI–HEMA 30	0.80	Synd.	0.70	0.04	36000	18
MEI–HEMA 30	0.76	Synd.	0.58	0.05	35000	26

[a] HEMA molar fraction in the copolymer obtained by ^{1}H-NMR.
[b] Isotacticity parameter obtained from the NMR analysis.
[c] MAI or MEI (M) centred molar fraction as calculated from the reactivity ratios.
[d] Number average molecular weight as obtained from GPC.
[e] Equilibrium swelling degree calculated as described in Materials and methods.

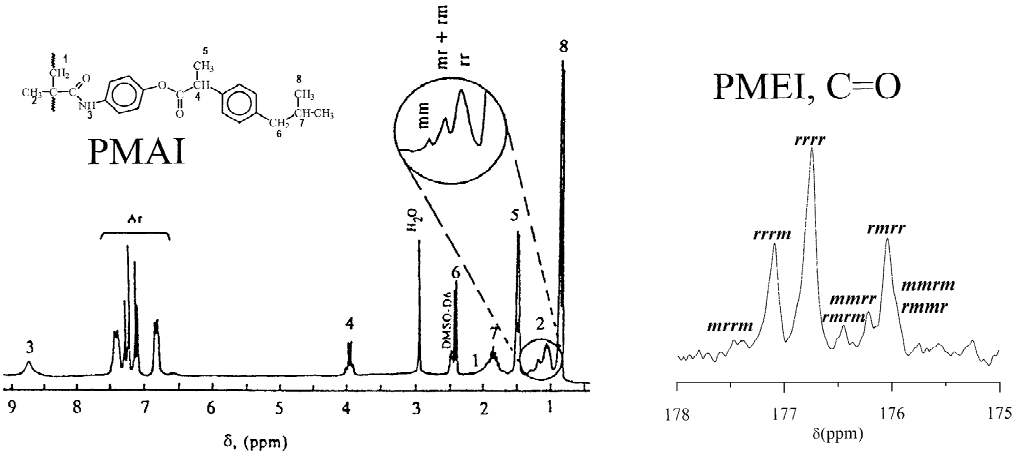

Fig. 4. ^{1}H NMR spectra of the homopolymer PMAI (left hand side) and expanded decoupled spectrum of the carbonyl carbon closer to the backbone for PMEI (right hand side).

Román, 1994). The oversimplified syndiotactic structures of two hexads are drawn for the homopolymer poly-MAI and the copolymer MAI–HEMA. We have not determined the isotacticity parameter for the copolymers but they are expected to be likely syndiotactic since poly-HEMA has a $\sigma = 0.22$. In any case, there is a higher rigidity and a more compacted packing in the homopolymer compared to the copolymer structure as a consequence of the presence of the aromatic groups and the long hydrophobic residues in the homopolymer and the short oxyethylene moieties of HEMA in the copolymer. The critical point, however, is the much higher hydrophobicity of the homopolymers: the equilibrium swelling degrees of the rich-HEMA copolymers are close to 20% while for the homopolymers are lower than 2%. Moreover, Fig. 5 shows schematically the easier accessibility to the active residues in the copolymers compared to the well-packed homopolymer structure.

Table 1 shows, in addition, the M (MAI or MEI) centered triad molar fractions for the two copolymers calculated from the reactivity ratios, $r_{MAI} = 0.38$, $r_{HEMA} = 1.69$ and considering $r_{MEI} \sim 1$ and $r_{HEMA} \sim 1$ as they are structurally very related (Gallardo et al., 2001). The theoretical sequence distributions for these particular compositions, calculated as described elsewhere (Gallardo and San Román, 1993b), are quoted in columns 4 and 5 (HMH and MMM triads), leading to the conclusion that the active residues are mainly surrounded by HEMA units. Thus, the molecular environment of the ibuprofen derivative is clearly more hydrophilic in the copolymers than in the homopolymers and significant differences in the release rates should be expected. This is the reason why we used, during in vitro studies, films for the copolymers and fine dispersed powder for the homopolymers, trying in this way to maximize the active surface area in order to obtain measurable quantities of *R*- and *S*-IBU from the hydrolytical experiments. A last point to be taken into account is the change in hydrophilicity with the release, since the residual unit (an OH group) is more hydrophilic that the parent active unit. This fact will influence the release kinetics, especially at high hydrolysis degrees, because the increase in hydrophilicity obviously allows a higher swelling and a faster hydrolysis.

3.3. In vitro drug release experiments

The release profiles from the copolymers at pH 7.4 and rat plasma are shown in Fig. 6 (for the *R*-IBU enantiomer). Fig. 7 exhibits the release of the *R*-IBU form at pH 10. The results obtained with the homopolymers are summarized in Fig. 8. The release profiles have been depicted as mg drug/g polymeric device in the three figures, but some release percentages have been added as a reference on the right hand side.

As it could be expected, the release rates from the more hydrophilic copolymers are much higher (about one order of magnitude) than from the hydrophobic homopolymers, which is in agreement with the aforementioned different accessibility of the medium to the labile ester bond. In fact, at pH 7.4 the homopolymers show releases lower than 0.1% in 2 months, while the copolymers exhibit a release up to 2% during the same period. In spite of this very slow release, one interesting property of this kind of system is that they present activity as ‘polymeric drugs’. It means that in a similar way to that of a great number of proteins, polysaccharides and other high molecular weight macromolecules, the polyacrylic systems present anti-inflammatory and antinociceptive activities in a very short time after application (Liso et al., 1995). This guarantees a long pharmacological effect in local points, i.e. by injection of suspensions into the joint cavities. Therefore the slow release can be beneficial for chronic treatments with the guarantee of final clearance of the support after long periods (several months).

The release at pH 10 is logically higher than at pH 7.4 (due to the well-known lability of the ester bonds in basic media). The pseudosigmoid shape of the release profiles at

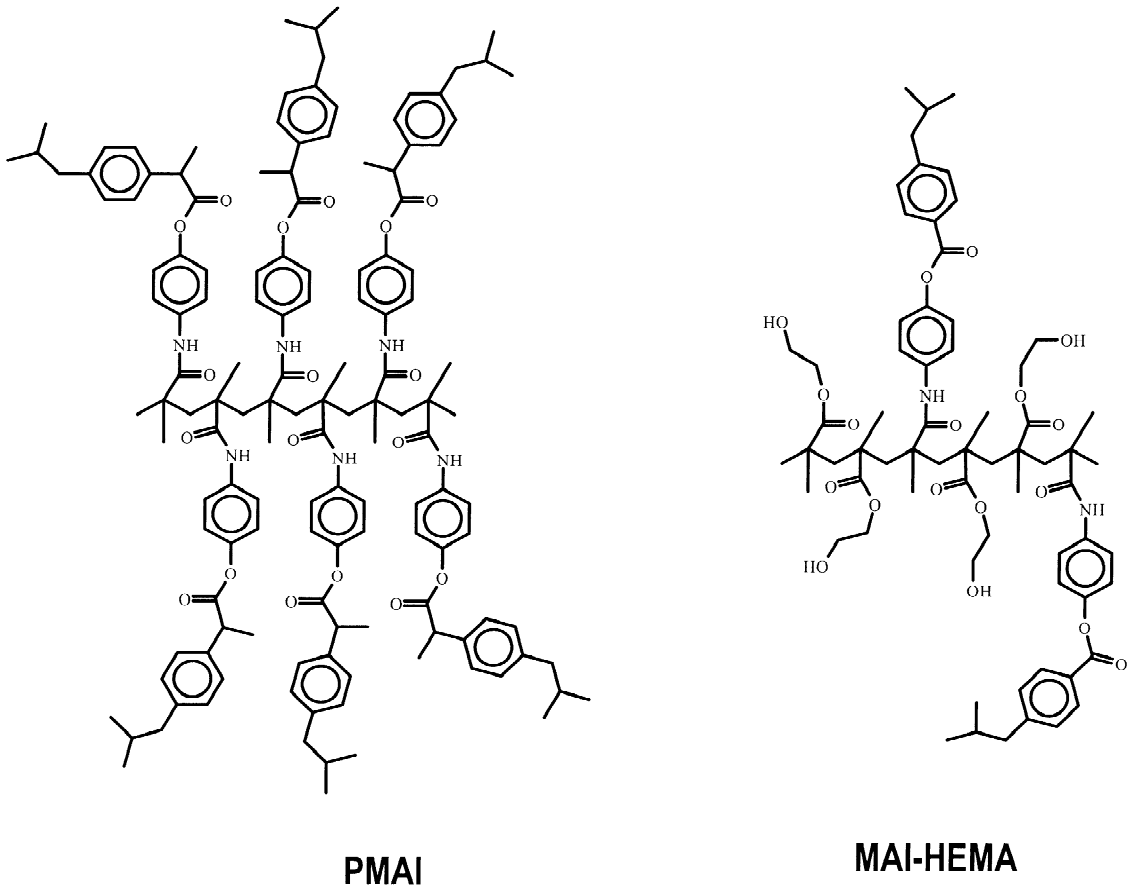

Fig. 5. Schematic structures of homopolymer (PMAI) and copolymer (MAI–HEMA) syndiotactic sequences.

pH 10 (Fig. 7) can be ascribed to the mentioned increase of hydrophilicity at high release rates as in this case.

On the other hand, the hydrolytical reactivity of the aromatic ester in MAI is clearly higher than the reactivity of the aliphatic group in MEI, in agreement with previous results (Gallardo et al., 2001). This different behavior is especially relevant in the case of the homopolymers (Fig. 8), despite the higher flexibility of the oxyethylenic spacer residue, and in the release at pH 7.4 from the copolymers (Fig. 6). In the case of the homopolymers, poly-MEI tends to aggregate forming hydrophobic particulates while poly-

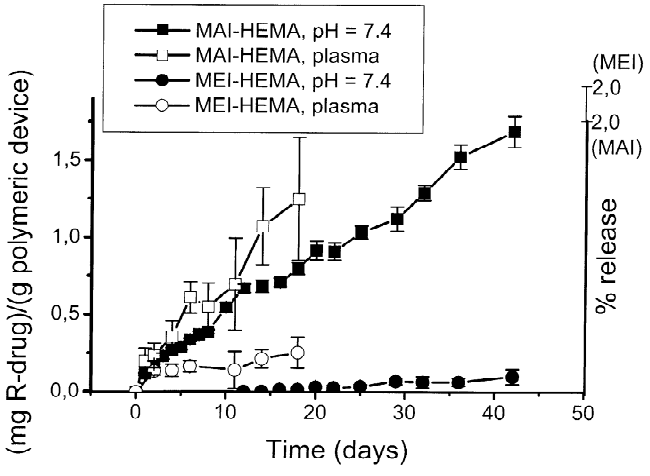

Fig. 6. Release profiles of *R*-IBU from the copolymers at pH 7.4 and plasma. The 2% releases are indicated as a reference in the right hand side of the figure for both types of systems.

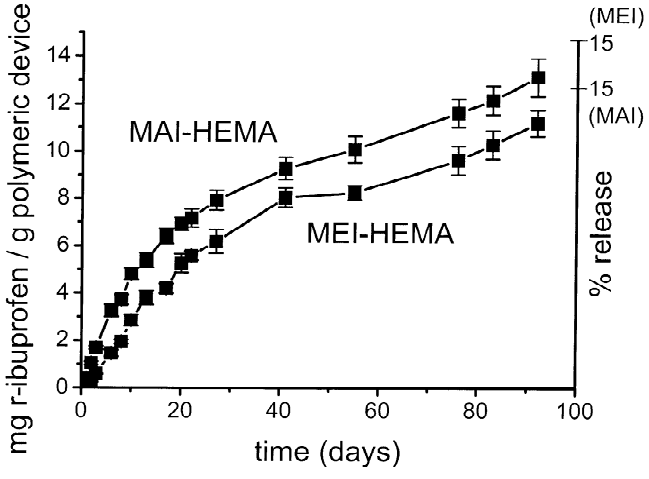

Fig. 7. Release profiles of *R*-IBU from the copolymers at pH 10. The 15% releases are indicated as a reference in the right hand side of the figure for both types of systems.

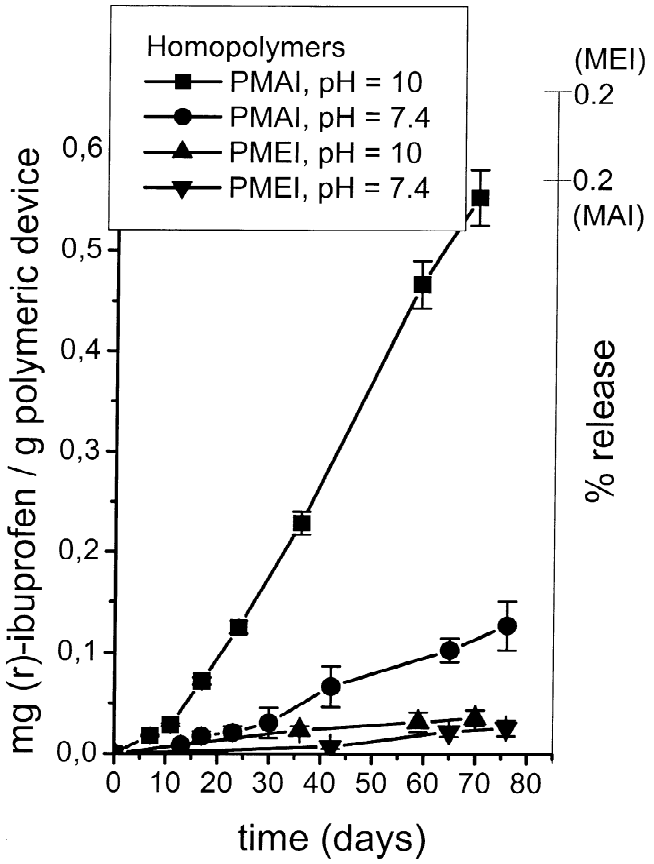

Fig. 8. Release profiles of *R*-IBU from the homopolymers at pH 7.4 and 10. The 0.2% releases are indicated as a reference in the right hand side of the figure for both types of systems.

MAI forms a stable dispersion and makes slightly easier the water accessibility to the ester bond. This point has to be added to the described higher reactivity of the aromatic ester.

The in vitro plasmatic experiments showed an interesting activation compared to the data at pH 7.4, demonstrating the occurrence of some kind of enzymatic activity. The MEI–HEMA system shows a release rate ca. 15 times higher in plasma than in buffer, while the MAI–HEMA is only two times higher. This activation can be related to the higher flexibility of the aliphatic spacer in MEI compared to the aromatic residue in MAI where in addition the side chain is linked to the backbone by means of a rigid amide group. This higher release rate was also obtained for the homopolymers, although these data are not shown for the sake of clarity.

The CE monitoring of the *R*- and *S*-IBU release provided interesting information. In most of the experiments, there is a slight excess of the active *S*-IBU form, which is particularly important in the case of the highest release rates, that is, the release from the copolymers at pH 10. In this sense, the enantiomeric excess of these samples, expressed as *S*-IBU/*R*-IBU ratio, is represented in Fig. 9 as a function of time. There is a tendency towards an *S*/*R* ratio of 1.05–1.10, which could be related to a higher ester

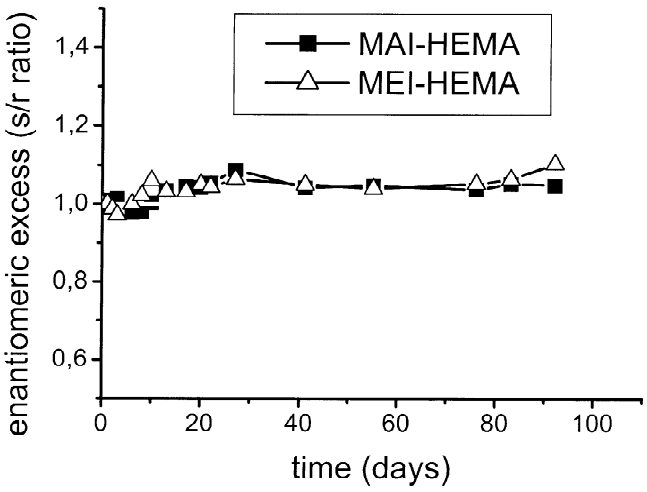

Fig. 9. *S*/*R* enantiomeric ratio as a function of time for IBU enantiomers released from the copolymers at pH 10.

reactivity of the *S*-form. It has to be noted that the plasma experiments did not exhibit a shifting to a higher biotransformation into the *S* form.

In conclusion, the usefulness of this method to quantitatively monitor the release of *R*(−)- and *S*(+)-IBU from different polymeric delivery systems has been demonstrated. It is shown that the release rate of IBU from the polymeric device depends on the hydrophilicity and on the spacer of the side residue and also, it is demonstrated that the release of both enantiomers is enzymatically activated in rat plasma. Slight enantiomeric excess has been found in most of the experiments, ranging from 1.05 to 1.10. This excess does not seem to be influenced by the enzymatic nature of the media.

Acknowledgements

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