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Controlled release of NSAIDs bound to polyacrylic carrier systems

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The synthesis, characterization and properties of new acrylic ''polymeric drugs'' derived from the NSAIDs agents ibuprofen and ketoprofen are described. The swelling behavior in hydrated medium and the controlled release from hydrophilic copolymers of the NSAIDs derivatives and 2-hydroxyethylmethacrylate, HEMA, are discussed, considering the hydrolytical reactivity of the acrylamide or acrylic ester functional groups, the aromatic or aliphatic structure of the spacer side groups, and the hydrophilic character of the copolymer systems. The results obtained demonstrated that the swelling degree of copolymers depends on the average composition of copolymers, decreasing with the increase of the average fraction of the corresponding acrylic derivative of ibuprofen or ketoprofen in the copolymer system. In addition, polymers which support the NSAIDs active component through aromatic amide links, are more sensitive to hydrolytical processes than those of alkyl ester functions. The results obtained demonstrate that these supports could be applied for direct administration, transdermal, systemic or intra-articular injection, as well as in the form of films on wounds. © *1998 Kluwer Academic Publishers*

1. Introduction

The enormous interest which has emerged in controlled delivery systems and targeting based on macromolecular formulations, has been the logical response to the excellent properties and behavior demonstrated for a variety of polymeric systems which provide good biocompatibility and biotolerance, excellent biodisponibility and sustained controlled release of a great number of drugs, and in some cases, adequate biodegradation [1–5].

In addition, from the pioneering work by Ringsdorf [6], the design of the polymeric drug delivery systems as targeting elements and as pharmacologically active formulations, has provided new and attractive solutions for complicated and chronic therapies, with relatively high toxic risk [2, 7–9]. These tailor-made systems present interesting possibilities because of the combination of properties such as hydrophilic or hydrophobic character, control of hydrolytical reactivity in hydrated media, or even specific interactions with enzymes and receptors. The application of "polymeric drugs" is also interesting, because they can act as macromolecular drugs or prodrugs with specific pharmacological activity and, in addition, if the active component is bound to the polymeric backbone, can be considered as a chemically controlled drug-delivery system, with the advantage that after the hydrolytic release of the active component, the polymeric matrix becomes soluble in the physiological medium, and if it has the adequate molecular weight, the clearance of the polymer is guaranteed.

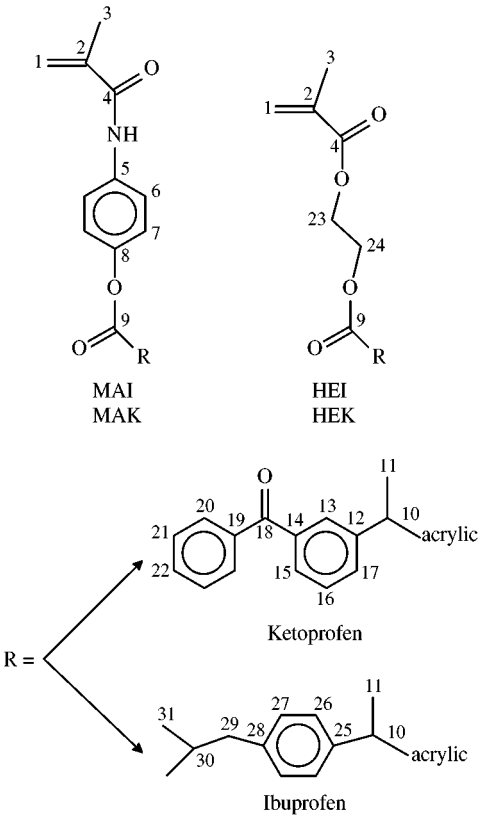
According to this principle, we have studied the preparation and application of various polymeric drugs based on acrylic derivatives of analgesic compounds such as salicylic acid or paracetamol [2, 10], as well as other non-steroidic anti-inflammatory agents NSAIDs based on derivatives of phenyl acetic or propionic acids [11, 12].

In this article, the comparative study of the hydrolytical behavior of polymeric drugs based on acrylic copolymers bearing two well-known NSAIDs, ibuprofen and ketoprofen, is reported. Hydrophilic properties of copolymers, as well as the reactivity of ester and amide side groups used as weak links between the drug and the polyacrylic matrix, are considered on the basis of results obtained *in vitro* at different pHs.

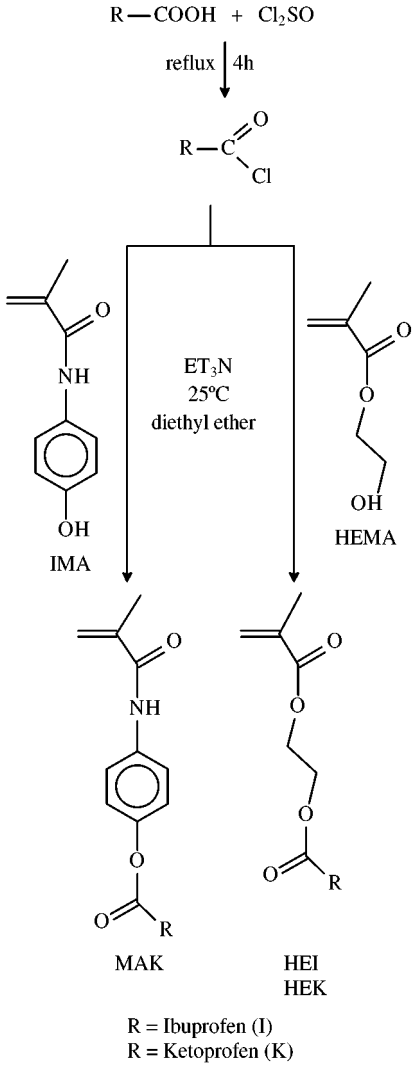
2. Materials and methods

2.1. Monomer synthesis

Structures of the different monomers are presented in Scheme I. Synthesis of intermediate reagents and synthetic route of MAI are described elsewhere [12]. MAK, HEK and HEI were prepared by a two-step route involving well-known organic reactions according to Scheme II. The first step was the preparation of the acid chloride derivative of ibuprofen and ketoprofen by reaction with thionyl chloride. In a typical experiment, 0.1 mol ibuprofen or ketoprofen was added to 70 ml thionyl chloride and the mixture was stirred under reflux for 4 h. The thionyl chloride excess



Scheme I.



Scheme II.

was removed by distillation. The acid chlorides were isolated by distillation under high vacuum (b.p. ibuprofen derivative = 110 °C/0.1 Hg mm, b.p. ketoprofen derivative = 170 °C/0.1 Hg mm); yield 95% and 91% respectively. The second step was an esterification reaction of HEMA or IMA with the acid chloride derivatives: 0.025 mol HEMA or IMA were dissolved in acetone and added to a solution of 0.025 mol triethylamine on diethyl ether. To this solution the acid chloride derivatives dissolved in diethyl ether (0.025 mol) were added dropwise. The reactions under nitrogen flux and at room temperature were kept for 24 h under magnetic stirring. The precipitated triethylamine chlorhydrate was removed by filtration. The filtrate was washed with an aqueous solution of NaOH (5% wt/vol) and the residual organic phase was dried over $MgSO_4$. The solvent was removed under vacuum until constant weight. Yield: 65% for MAK, 88% for HEI and 75% for HEK.

2.2. Polymerization

Polymers and copolymers were prepared by the free radical polymerization of a mixture of the corresponding monomers in *N*,*N*-dimethyl formamide (DMF) at high vacuum and 50 °C. 2,2-azobisisobutironitrile, AIBN, was used as initiator.

2.3. Swelling experiments

The absorption of water was followed gravimetrically by measuring the weight uptake of dry thin films (~ 0.5 mm thick) immersed in a buffered solution (pH = 7) at 37 °C. Films were obtained by casting from isopropanol/DMF solutions (1:1).

2.4. In vitro drug release

Pieces of 1, 1.5 cm^2 of loaded films were engaged in a stainless steel mesh and they were immersed in buffered solutions at pH 7 and 9 with 0.1% wt/wt Tween 80 (sink conditions), and 37 °C; the solution was periodically collected for analysis and replaced by the same volume of fresh medium. The amount of ibuprofen and ketoprofen in the medium was determined by UV spectroscopy; λ_{max} = 263 and 261 nm, respectively.

3. Results and discussion

MAK, HEI and HEK were synthesized according to Scheme II or following the synthesis route described elsewhere [12] in the case of MAI. These monomers were characterized by IR, ^1H and ^{13}C-NMR spectroscopies; Figs 1 and 2 show the assigned ^{13}C-NMR spectra of the products (identification numbers correspond to those drawn in Scheme I). Polymers and copolymers were synthesized at 50 °C by a free radical

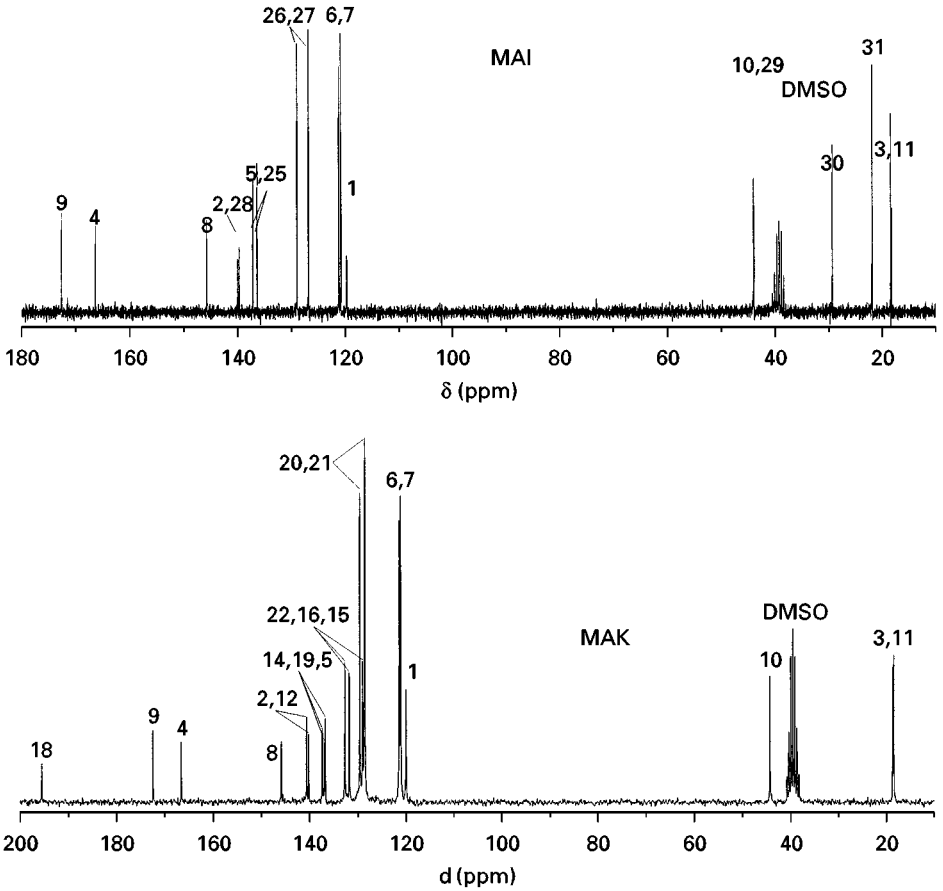


Figure 1 Decoupled ^{13}C-NMR (50 MHz) spectra of MAI and MAK in DMSO-d_6.

mechanism in DMF solution and using AIBN as initiator. They were characterized by ^{1}H and ^{13}C-nuclear magnetic resonance (NMR) spectroscopy, differential scanning calorimetry (DSC) and gel permeation chromatography (GPC). The average molecular weights, $\bar{M}_n$, of the polymers isolated by precipitation; oscillate between 50 000 and 100 000 Daltons obtained by GPC and referred to polystyrene standards.

The flexibility of polymers and the possibility for local or cooperative motions are of great importance in drug release, as well as on the aqueous behavior in hydrated media of chemically linked drug-delivery systems, such as the polyacrylic systems that are described in this work. A very useful parameter to measure qualitatively these characteristics is the glass transition temperature, T_g. In this sense, the T_g/s of the monomers and homopolymers are shown in Table I. It can be seen that, while the differences in T_g values for monomers are negligible, the T_g/s of polymeric derivatives of methacrylamide, PMAI and PMAK are about 50 °C higher than that of the corresponding polyacrylic esters, PHEI and PHEK. This is associated with their macromolecular nature because of the macromolecular structure involving steric restrictions in the chain motions and therefore in the mobility of the side residues for high molecular weight polymers. These differences can be related to the dipolar interactions of the aromatic methacrylamide group, because the corresponding aliphatic diesters show T_g values remarkably lower, which means a noticeably higher chain mobility. Moreover, the oxyethylenic spacer of HEI and HEK units, gives additional flexibility in comparison with the aromatic structure of the 1,4 disubstituted benzyl ring in MAI and MAK units (see Scheme I).

The copolymerization reactions with HEMA lead to random copolymers with a statistical distribution of the units along the macromolecular chains and they fit the classical terminal model with calculated reactivity ratios for the MAI-HEMA and MAK-HEMA systems of $r_{MAI} = 0.38$, $r_{HEMA} = 1.69$ and $r_{MAK} = 0.30$, $r_{HEMA} = 0.49$, respectively. The HEI-HEMA and HEK-HEMA systems are expected to be closer to ideal copolymerization systems (with reactivity ratios close to 1), as a consequence of the similar reactivity of the methacrylic residues and their structure (in fact, HEI and HEK can be considered HEMA derivatives, Schemes I and II). The more interesting copolymeric systems for applications as controlled delivery systems or targeting formulations, are those rich in HEMA component, because it is in this range where the macromolecules have an adequate hydrophilic character and therefore offer the higher compatibility with the physiological medium. From the microstructural analysis, we can consider that the distribution of repeating units is statistical, and for the studied composition, the active component should be placed preferably in the copolymer chains isolated by HEMA segments.

These copolymer systems are amorphous and lead easily to transparent films which have been used for *in vitro* experiments. Figs 3 and 4 show the equilibrium

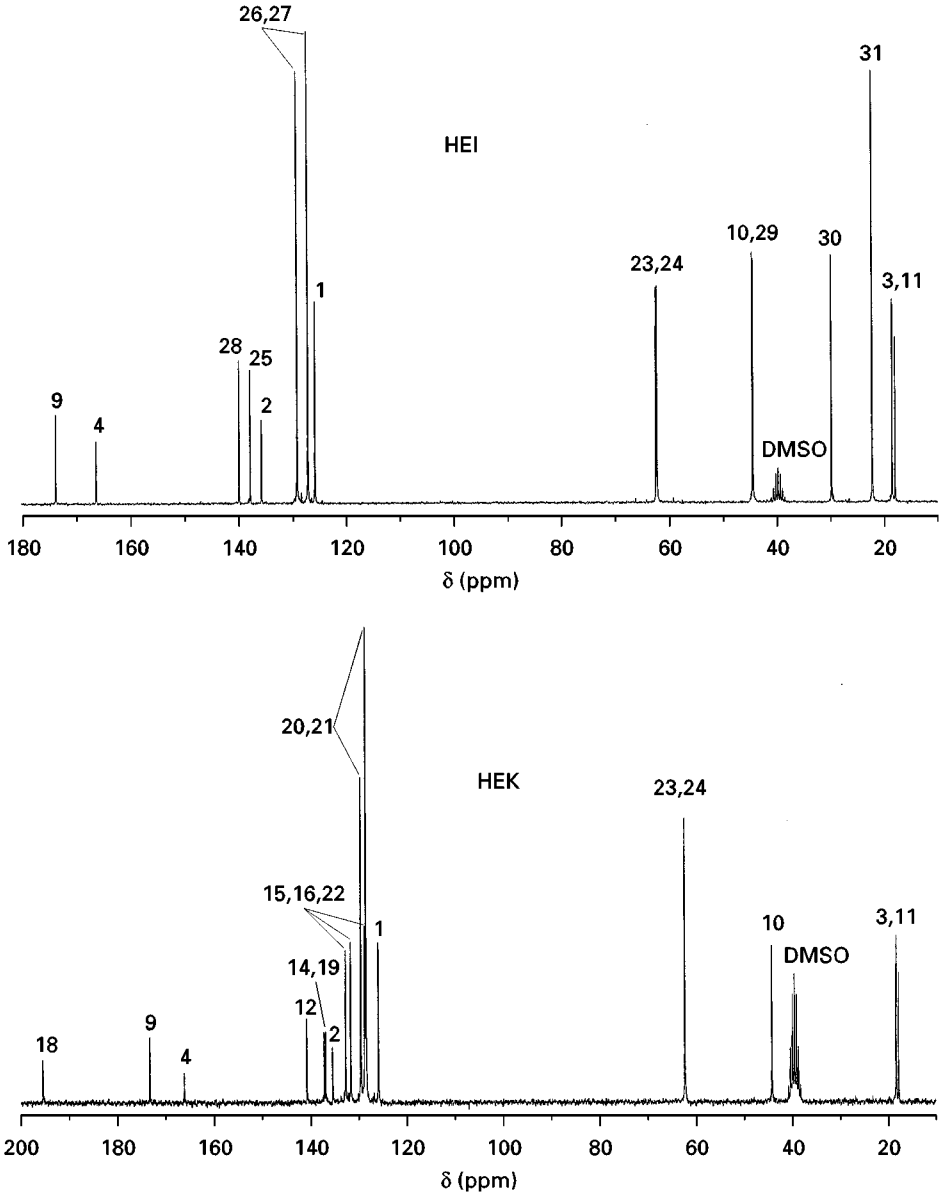


Figure 2 Decoupled ^{13}C-NMR (50 MHz) spectra of HEI and HEK in DMSO-d_6.

TABLE I

Compound	T_g (°C)	$\Delta T_g = T_{gPOD} - T_{gMON}$ (°C)
Monomers		
MAI	0	–
MAK	−8	–
HEI	−19	–
HEK	−10	–
Polymers		
PMAI	85	85
PMAK	94	102
PHEI	24	43
PHEK	40	50

swelling degree (defined as [wet weight-dry weight +]/ wet weight) for the aliphatic (HEI-HEMA and HEK-HEMA) and for the aromatic systems (MAI-HEMA and MAK-HEMA), respectively. They correspond to

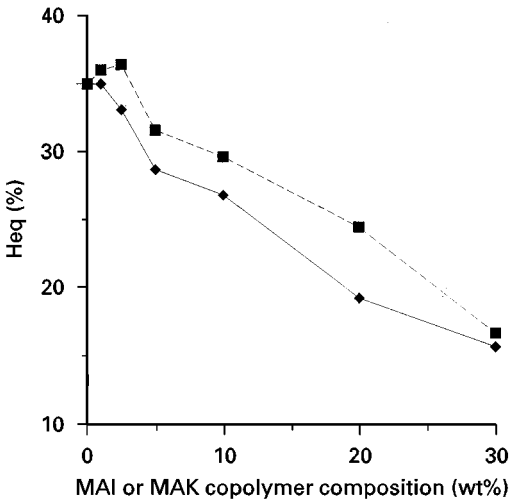


Figure 3 Equilibrium swelling degree (%) of the systems (◆) MAI-HEMA and (■) MAK-HEMA as a function of the MAI or MAK copolymer composition (wt %), respectively.

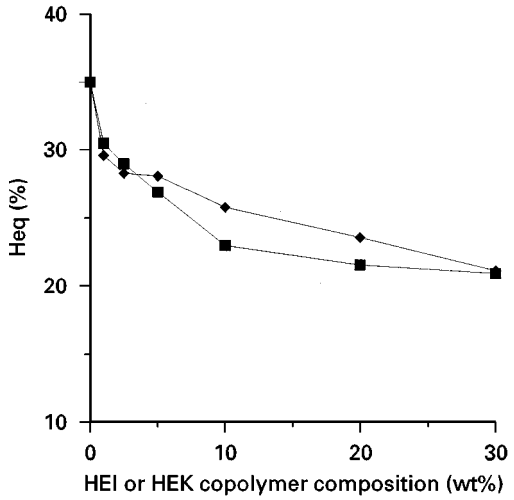


Figure 4 Equilibrium swelling degree (%) of the systems (◆) HEI-HEMA and (■) HEK-HEMA as a function of the HEI or HEK copolymer composition (wt %), respectively.

copolymer systems with different active compound contents (1–30 wt %). The swelling degree reached a maximum in a few hours and these equilibrium degrees decrease with the active compound content because of the increasing hydrophobicity, as has been described for similar copolymer systems [13], although the two systems exhibit a slightly different behavior. At very low composition of the active unit (1–2.5 wt %), the aromatic system (Fig. 4) have a similar or even higher swelling than PHEMA ($H_{eq} = 35\%$ according to Huglin and Sloan [14]), while the aliphatic systems show a clear decrease in water uptake. However, the evolution with composition shows that the swelling in aromatic ester–amide systems decreases faster than in the aliphatic diester systems with the increase in active components. This behavior has to be related to the presence of a high polar hydrogen in the amide group in MAI and MAK, which would be responsible for the water uptake at these low compositions, while for the other cases, the global hydrophobic/hydrophilic balance and the flexibility of the residues have to be taken into account.

The hydrolytic release tests were carried out on films of copolymer systems prepared with different composition, from 1–30 wt % active component, UV spectroscopy was used to measure the concentration of the released side residue in buffered solutions at pH 7 and = 9 at 37 °C. Under these experimental conditions, the films are not disintegrated when a stainless steel net is used as a physical support. This guarantees that no polymeric species are incorporated into the solution and the film remains in a highly swollen state. Figs 5 and 6 show the cumulative release percentage of the aromatic and aliphatic ketoprofen derivatives, respectively. The copolymer systems bearing the ibuprofen moiety showed a similar behavior. The release rate is intimately related to the swelling behavior,

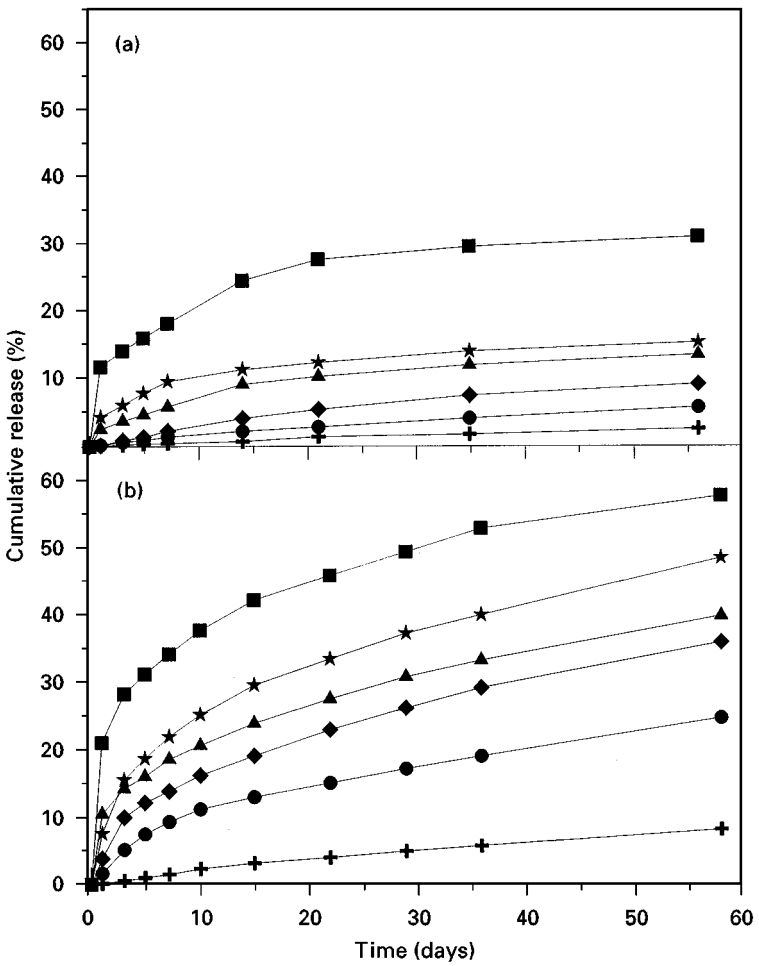


Figure 5 Ketoprofen release profiles of MAK-HEMA films at (a) pH = 7 and (b) pH = 9 for copolymers with different MAK weight compositions (%): (■) 1.0, (★) 2.5, (▲) 5.0, (◆) 10, (●) 20 and (+) 30.

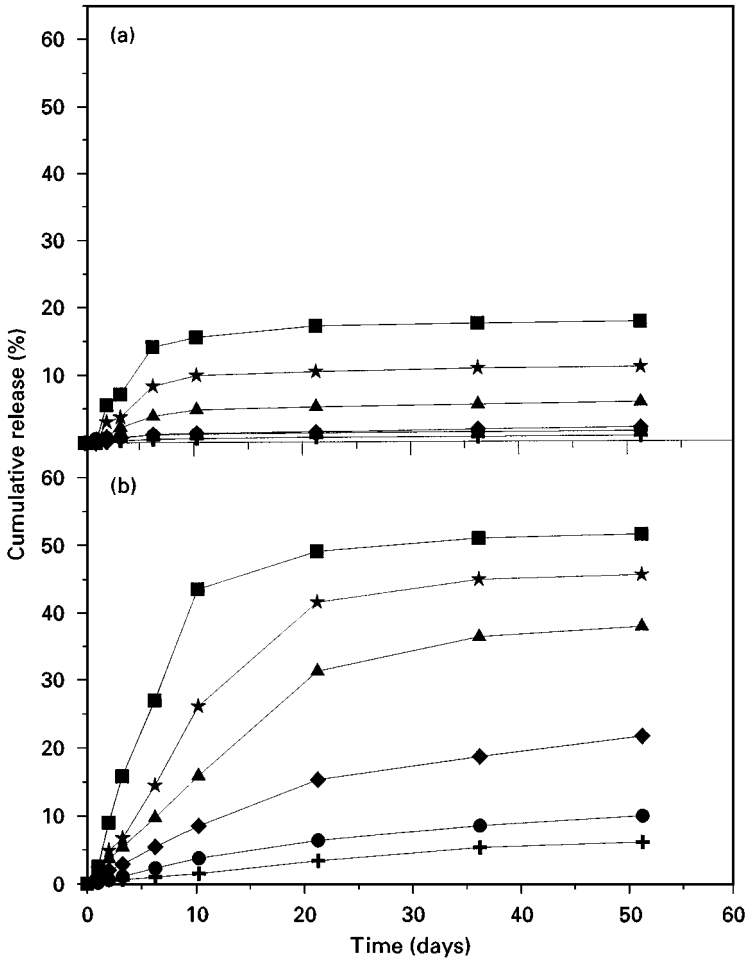


Figure 6 Ketoprofen release profiles of HEK-HEMA films at (a) pH = 7 and (b) pH = 9 for copolymers with different MAK weight compositions (%): (■) 1.0, (★) 2.5, (▲) 5.0, (◆) 10, (●) 20 and (+) 30.

showing the copolymer richest in active monomer has the slowest hydrolysis rate, due to the higher hydrophobic character, as has been described for similar systems [11]. On the other hand, the chemical structure of the spacer, aromatic ester–amide or aliphatic diester, is of great importance in the hydrolytic behavior. With respect to the chemical nature of the functional organic groups, the aromatic ester–amide systems show a faster release because of the presence of the more sensitive amide group, and moreover they show a higher sensitivity to the pH (Figs 5 and 6). This fact has to be associated to the catalytic effect of the alkaline reagent on the amide group. On the other hand, the release of the drug observed at pH 7 without any catalyst, indicates that the enzymatic activity can be important in these systems, because esterases and amidases in particular are effective in close neutral conditions.

4. Conclusions

The synthesis of new acrylic derivatives of classical and well-known NSAIDs agents, derived from phenylpropionic acid, ibuprofen (MAI and HEI), and ketoprofen (MAK and HEK), are proposed. Their corresponding polymerization by a free-radical polymerization mechanism, provides high molecular weight biocompatible acrylic polymers with excellent properties as "polymeric drugs" and controlled delivery systems. The copolymerization of these monomers with the highly hydrophylic acrylic compound HEMA gives rise to the formation of a family of copolymeric systems with hydration properties and *in vitro* drug-delivery behavior controlled by the chemical nature of the acrylic side functional bonds, and the spacer group between the polymeric support and the active drug. In addition, the hydrophilic characteristics and the release rate are controlled by the composition of the copolymer chains.

In all cases, amorphous, highly swollen systems with excellent biocompatibility in a hydrated medium are obtained. They can be applied as macromolecular delivery systems for oral, systemic, or transdermal administrations, as well as intra-articular injections, to have a sustained anti-inflammatory and analgesic action in local points of the organism. Applications in transdermal and intracuticular administrations, as well as in the form of films in wounds, are being tested in rats and rabbits.

Acknowledgments

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