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International Journal of Pharmaceutics 316 (2006) 68–73
INTERNATIONAL JOURNAL OF PHARMACEUTICS
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Synthesis and study of controlled release of ibuprofen from the new acrylic type polymers

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Received 24 July 2005; received in revised form 15 February 2006; accepted 18 February 2006
Available online 6 March 2006

Abstract

New acrylic type polymeric systems having degradable ester bonds linked to ibuprofen were synthesized and evaluated as materials for drug delivery. Methacryloyloxy(2-hydroxy)propyl-4-isobutyl-α-methylphenyl acetate (MOPE), a new methacrylic derivative of ibuprofen in which the drug is separated from the methacrylic backbone by an oxy(2-hydroxy)propylene spacer arm and hydrolytically labile ester bond, was synthesized from reaction of glycidyl methacrylate with ibuprofen. The resulting drug containing monomer was copolymerized with methacrylamide, 2-hydroxyethyl methacrylate, *N*-vinyl-2-pyrrolidone or *n*-butyl methacrylate by free radical polymerization method in *N*,*N*-di-methylformamide (DMF) solution, utilizing azobisisobutyronitrile as initiator at the temperature range 65–70 °C. The obtained polymers were characterized by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy. Gel permeation chromatography (GPC) was used for determination of average molecular weights of drug–polymer conjugates and showed that the polydispersity indices of the polymers are in the range of 1.9–2.3. Drug release studies were performed by hydrolysis in buffered solutions (pH 1 and 8) at 37 °C. Detection of hydrolysis by UV spectroscopy at selected interval showed that the drug can be released by selective hydrolysis of the ester bond at the side of drug moiety. The release profiles indicated that the hydrolytic behavior of polymeric prodrugs is strongly based on the hydrophilicity of polymer and the pH of the hydrolysis solution. The hydrophilic polymers containing ibuprofen were hydrolyzed in buffer solutions rather than the hydrophobic polymers.

Keywords: Ibuprofen; Acrylic polymers; Polymeric prodrugs; Controlled release

1. Introduction

A major approach to increasing the therapeutic efficiency of bioactive agents while decreasing their toxicity has involved their chemical attachment to synthetic or naturally occurring macromolecules (Ringsdorf, 1978). Thus, various agents have been bound via degradable linkages to many different polymeric systems. These systems are hydrolyzed in the body, releasing drug at a predetermined rate (Banker, 1984). Functional polymers containing bioactive agents as pendent groups are produced either by chemical modification of preformed polymers, or by direct (co)polymerization of the desired functional monomers with suitably chosen structural monomers (Boudreaux et al., 1996; Levenfeld et al., 1990). Drugs that contain reactive functional groups such as carboxyl or hydroxyl groups can be converted to a wide variety of polymerizable derivatives. The majority of the drug monomers that have been polymerized are acrylic type derivatives of pharmaceutically active compounds (Akashi et al., 1987; San Roman and Levenfeld, 1990; Davaran et al., 1999; Mahkam and Sharifi-Sanjani, 2003).

The therapeutic use of non-steroidal anti-inflammatory drugs (NSAIDs) is often restricted by the necessity to deliver the drug to specific sites of target organ or tissue. The use of NSAIDs is also limited by their irritant side effects on the gastro-enteric mucosa and by their frequent poor water solubility (Giammona et al., 1989). These problems can be solved by the preparation of polymeric prodrug backbones via hydrolyzable bonds. Polymer–drug conjugates of NSAIDs have been developed in order to minimize delivery problems and reduce gastrointestinal side effects by controlling the rate, duration and site of release. These polymeric prodrugs have been designed for localized and prolonged duration of drug action by parental administration, or as dermal prodrugs (Bonina et al., 1995).

Ibuprofen, 2-(4-isobutylphenyl)propanoic acid, as a NSAID is widely used for the treatment of rheumatoid arthritis. Its side effects (especially the gastric irritation) are less than aspirin.

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doi:10.1016/j.ijpharm.2006.02.032

In recent years, some NSAIDs such as ibuprofen (Davaran and Entezami, 1997a, 1998; Chang et al., 1998; Kim et al., 2005), indomethacin (Davaran and Entezami, 1997b; Kim et al., 1998), naproxen (Bonina et al., 2001), ketoprofen (Chang et al., 1998) and diclofenac (Nasir Tabrizi et al., 1996; Namazi et al., 2001) were covalently attached to various polymer backbones and their hydrolysis studied.

This article reports the synthesis and in vitro evaluation of acrylic type polymeric prodrugs of ibuprofen. Methacryloyloxy(2-hydroxy)propyl-4-isobutyl-α-methylphenyl acetate (MOPE), as a new monomer-containing drug, was prepared using activated ester methodology. The copolymers of MOPE with methacrylamide (MAAm), 2-hydroxyethyl methacrylate (HEMA), *N*-vinyl-2-pyrrolidone (NVP) and *n*-butyl methacrylate (BMA) were prepared by free radical polymerization technique. The release of ibuprofen from polymeric prodrugs was studied in vitro by hydrolysis in buffered solutions at different pH values. Some factors influencing the degradation of polymers, such as the neighboring effect of co-monomers, the effect of the spacer group and the pH of hydrolysis solution are discussed.

2. Materials and methods

2.1. Instrumental measurements and materials

FT-IR spectra were recorded by use of KBr pellets on a Shimadzu 4300 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometer in $CDCl_3$ or DMSO-d_6 solution. The amount of released drug was determined by a 2100 Shimadzu UV spectrophotometer at the adsorption maximum of the free drug in aqueous buffered solutions (λ_{max} = 264 nm) using a 1 cm quartz cell. Molecular weights of polymers were determined with a Maxima 820 GPC analysis instrument (mobile phase, DMF; run time, 50 min; column temperature, 50 °C). Well-characterized polyethylene oxide was used in the calibration within the range of M_w between 2600 and 885,000. Elemental analysis was carried out with a Heareus CHN-ORAPID instrument. Melting points were determined on a 9100 Electrothermal apparatus. The cellophane membrane dialysis bag, with a molecular weight cut-off 2000 (Sigma, St. Louis), was used as provided.

Ibuprofen was purchased from Aldrich. MAAm, HEMA, NVP, BMA and glycidyl methacrylate (GMA) were obtained from Merck. Azobisisobutyronitrile (AIBN) was obtained from Fluka and crystallized from methanol. *N*,*N*-Dimethylformamide (DMF) was dried over anhydrous $MgSO_4$ for 2 days and distilled under reduced pressure. All other chemicals were reagent grade or purer.

2.2. Synthesis of methacryloyloxy(2-hydroxy)propyl-4-isobutyl-α-methylphenyl acetate

A mixture of 5.39 g (38 mmol) of GMA, 7.82 g (38 mmol) of ibuprofen, 0.38 g of hydroquinone and 5 ml of pyridine were dissolved in 20 ml of DMF into a Pyrex glass ampoule. The ampoule was sealed under vacuum and shaken in a water bath at 40 °C for 6 h. The ampoule was then cooled and the resulting solution was poured in aqueous saturated $NaHCO_3$ solution (50 ml). The organic phase was separated by THF, dried with anhydrous $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was subjected to silica gel column chromatography. Elution with methanol:diethyl ether:chloroform (2:2:0.5, v/v/v) gave 6.7 g (51%) of monomer MOPE. FT-IR (KBr, cm^{-1}): 3350 (O–H), 3060, 3030 (=C–H), 2950, 2890 (C–H aliphatic), 1735 (unconjugated ester carbonyl), 1710 (conjugated ester carbonyl), 1630 (C=C vinyl), 1600 and 1470 (C=C aromatic). ^{1}H NMR ($CDCl_3$ with tetramethylsilane, ppm): 1.9 (s, 3H, =C(CH_3)), 3.6 (q, 1H, CH-aryl), 4.1 (m, 4H, OCH_2–C–CH_2O), 4.4 (m, 1H, CH–O), 5.1 (s, 1H, OH), 5.6–6.1 (d, 2H, CH_2=C), 7.1–7.6 (q, 4H, aryl-H). ^{13}C NMR ($CDCl_3$ with tetramethylsilane, ppm): 53.2 (2C, OCH_2), 56.5 (1C, OHCH), 116.2 (1C, CH_2=), 127.1, 128.3, 138.1, 145.2 (6C, aromatic carbons), 137.2 (1C, =C), 167.4 and 173.4 (2C, ester carbons). Elemental analysis for $C_{20}H_{28}O_5$ (348) (%): calcd. C 68.9, H 8.0; found: C 68.7, H 8.1.

2.3. Copolymerization, general procedure

In four Pyrex glass ampoules, a mixture of 1.74 g (5 mmol) of MOPE, 0.16 g (1 mmol) of AIBN, 1.27 g (15 mmol) of MAAm or 1.95 g (15 mmol) of HEMA or 1.66 g (15 mmol) of NVP or 2.13 g (15 mmol) of BMA was dissolved in 10 ml of dried DMF, respectively. The ampoules were then degassed, sealed under vacuum, maintained at 65–70 °C in a water bath and shaken by a shaker machine for about 48 h. After this time, the viscous solutions were separately poured from the ampoules into 150 ml of cooled methanol. The precipitates were collected, washed with methanol for several times and dried under vacuum at room temperature.

2.4. Method of hydrolysis

The copolymers were dried in vacuum at room temperature. Dried copolymer (200 mg) was poured into 5 ml of aqueous buffered solution (pH 1 and 8) at 37 °C. The mixture was conducted into a cellophane membrane dialysis bag. The bag was closed and transferred into a flask containing 25 ml of same buffer solution maintained at 37 °C. The external solution was continuously stirred and a 3 ml sample was removed at selected intervals and 3 ml of buffer was replaced. The quantity of released drug was analyzed by means of an UV spectrophotometer and determined from the calibration curve obtained previously under the same conditions.

2.5. Characterization of hydrolysis products

Twenty milligrams of the polymer–drug adduct was dispersed into 20 ml of buffered solution (pH 8) and maintained at 37 °C. After 24 h, the hydrolysis solution was sampled, neutralized with 1N HCl and the solvent was removed in vacuum. The resulting crude product was treated with 10 ml of acetone and heated. The suspension was then filtered and the acetone solution was evaporated under reduced pressure. The residue was characterized by

melting point measurement and IR spectroscopy. m.p. 77 °C. IR (KBr, cm^{-1}): 3400–2900 (O–H), 2950, 2870 (C–H aliphatic), 1725 (C=O), 1600, 1470 (C=C aromatic), 1230 (C–O). These results showed that the hydrolysis product is ibuprofen.

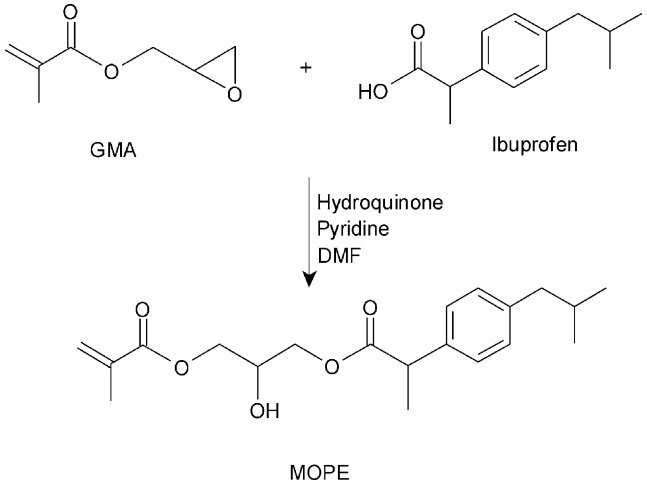
3. Results and discussion

3.1. Synthesis of polymerizable derivative of ibuprofen

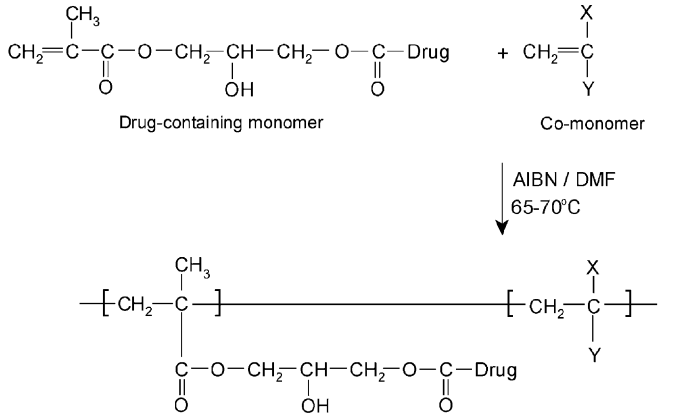
For preparation of polymerizable monomers pharmaceutically active compounds, it is necessary to use synthetic conditions mild enough to allow attachment without any adverse effect on the physiological activity of drug (Ringsdorf, 1975). Several lines of evidence suggested that the limited efficiency of polymeric prodrugs was a reflection of the limited loading and a too slow hydrolysis of the drug from the polymer backbone. The introduction of a spacer group between the drug and polymer chain, and employing the monomers instead of the performed polymers could eliminate these problems. Therefore, in this article a spacer arm was located between the drug and vinyl moiety. The acrylic type polymerizable derivative of ibuprofen was synthesized according to the synthetic route described in Scheme 1. The monomer-containing drug, MOPE, was synthesized by reaction of glycidyl methacrylate with ibuprofen in the presence of hydroquinone and pyridine. MOPE is an activated methacrylate, providing an active ester residue as a functional group precursor.

3.2. Synthesis of polymeric prodrugs

Drug containing monomer, MOPE, was easily copolymerized with MAAm, HEMA, NVP and BMA in dried DMF solution, by free radical technique at 65–70 °C using AIBN as the initiator (Scheme 2). The preparing conditions of copolymers are shown in Table 1. The resulted copolymers were colorless, amorphous and soluble in DMSO and DMF but insoluble in water and alcohols. The conversions of monomers to copolymer were determined gravimetrically after exhaustive drying of the isolated copolymer sample. This method permits the incorporation of 14–20 wt.% of ibuprofen into the copolymers (Table 2). The drug content of the copolymers and the required doses of the prodrugs, which are equivalent to 300 mg of ibuprofen, were calculated in Table 2.



Scheme 1.



X	CH_3	CH_3	H	CH_3
Y	$CONH_2$	$COOCH_2CH_2OH$		$COOCH_2CH_2CH_2CH_3$
Co-monomer	MAAm	HEMA	NVP	BMA

Scheme 2.

3.3. Characterization of polymeric prodrugs

Characterization data for the prepared polymers were obtained through a variety of techniques including FT-IR and NMR spectroscopy. The results confirmed the structure of the polymers. Spectral characteristics of functional groups of copolymers having ibuprofen substituent are given in Table 3.

Copolymer compositions were also determined from ^1H NMR spectroscopic data. In the past few decades, ^1H NMR spectroscopic analysis has been established as a powerful tool for the determination of copolymer compositions because of its simplicity, rapidity and sensitivity (Chang et al., 1998; Safa and Babazadeh, 2004; Safa et al., 2004). For example, the molar compositions of MOPE and MAAm units in poly(MOPE-*co*-MAAm) were calculated from the ration of the integration peaks around 7–8 ppm, corresponding to four aromatic protons from MOPE to area 9.9 ppm, corresponding to two amide protons of

Table 1
The preparation conditions of polymeric prodrugs

Sample	$[M_1]$ (mmol/L)	$[M_2]$ (mmol/L)	Conversion (%)
Poly(MOPE-*co*-MAAm)	MOPE (5)	MAAm (15)	71
Poly(MOPE-*co*-HEMA)	MOPE (5)	HEMA (15)	65
Poly(MOPE-*co*-NVP)	MOPE (5)	NVP (15)	62
Poly(MOPE-*co*-BMA)	MOPE (5)	BMA (15)	52

M_1, drug containing monomer; M_2, co-monomer; $[M_1]+[M_2]/[AIBN]=20$; solvent, DMF; temperature, 65–70 °C; time, 48 h.

Table 2
Characterization of drug containing copolymers

Sample	$M_n \times 10^{-3}$	M_w/M_n	M_1 (g%)	M_2 (g%)	D (g%)	P.D. (g)
Poly(MOPE-*co*-MAAm)	7.3	2.1	33	67	19.5	1.5
Poly(MOPE-*co*-HEMA)	6.0	1.9	29	71	17.1	1.7
Poly(MOPE-*co*-NVP)	4.8	2.3	31	69	18.3	1.6
Poly(MOPE-*co*-BMA)	5.6	1.9	25	75	14.8	2.0

M_n, number-average molecular weight; M_w, weight-average molecular weight; M_1, content of drug containing monomer (MOPE); M_2, content of co-monomer (MAAm, HEMA, NVP or BMA); D, content of ibuprofen in the copolymer; P.D., the prodrug doses equivalent to 300 mg of ibuprofen.

MAAm. The calculated compositions of polymeric prodrugs are presented in Table 2.

On parameter in characterization of polymeric prodrugs is determination of molecular weight distribution and the average molecular weights (Kuzuya et al., 1991). The weight and number-average molecular weights of the synthesized polymeric prodrugs were estimated by gel permeation chromatography (GPC). The values are shown in Table 2.

3.4. Drug release by hydrolysis of polymeric prodrugs

It has been widely demonstrated that the side chain hydrolysis of drug pendent polymers depends on the strength and chemical nature of the drug–polymer chemical bonds, the structure of the polymer and the surrounding condition. The hydrolysis of a linkage is also dependent on its distance from the polymer backbone. The length and hydrophilicity of the spacer unit between the drug and polymer chain can affect the release rate (Harris, 1984). The in vitro hydrolysis behavior of drug–polymer adduct was studied in physiological conditions (aqueous phosphate or hydrochloric acid buffers, at 37 °C). As the polymers were not soluble in water, they were dispersed in buffer solution and the hydrolysis was performed in a heterogeneous system. The hydrolysis was carried out in cellophane membrane bags permeable to low molecular weight compounds. The released drug passed through the high molecular weight polymers into the external buffer solution and determined by a UV spectrophotometer by noting its absorbance at 264 nm. Two hydrolysable ester bonds are present in polymers. Detection of the hydrolyzing solution by UV spectrophotometer showed that only the ester bond between drug moiety and spacer is hydrolyzed during the reaction time (24 h). The IR spectroscopic data and melting point measurements of the residue corresponded to the free drug. The direct ester linkage between the main chain of polymer and spacer arm is less susceptible towards the hydrolysis. This can be related to the steric hindrance of bulk polymer chains, which decrease the bond mobility.

Figs. 1 and 2 show the degree of hydrolysis of the polymers containing ibuprofen as function of time under mild conditions in HCl buffer (pH 1) and KH_2PO_4–Na_2HPO_4 buffer (pH 8), respectively. The order of hydrolysis was as follows:

Poly(MOPE-*co*-MAAm) > poly(MOPE-*co*-NVP) > poly(MOPE-*co*-HEMA) > poly(MOPE-*co*-BMA).

Different factors such as solubility of polymers and neighboring effect of side groups can affect the overall rate of hydrolysis. The hydrophilic copolymers containing ibuprofen were hydrolyzed in buffer solutions rather than hydrophobic copolymers. As shown in Figs. 1 and 2, the copolymer containing MAAm units was hydrolyzed rapidly because the MAAm units were more hydrophilic than the HEMA and NVP units. Therefore, poly(MPOE-*co*-MAAm) was easily hydrolyzed in comparison with poly(MOPE-*co*-NVP) and poly(MOPE-*co*-HEMA). Also, poly(MOPE-*co*-BMA) was hydrolyzed slowly because of hydrophobicity of BMA units in the copolymer.

Table 3
Spectral characterization of drug containing copolymers

Sample	Functional group	^{1}H NMR (ppm)	^{13}C NMR (ppm)	FT-IR (cm^{-1})
Poly(MOPE-*co*-MAAm)	COO	–	173.4	1733
	CONH	9.9	169.1	3300, 1680
Poly(MOPE-*co*-HEMA)	COO	–	174.1	1735
	OH	5.1	–	4200–3200
Poly(MOPE-*co*-NVP)	COO	–	173.8	1735
	NCO	–	176.5	1735
Poly(MOPE-*co*-BMA)	COO	–	173.5, 176.5	1733
All polymers	CH_2O	4.1	53.2	1100
	CHO	4.4	56.5	1090
	Ph	6.9–7.7	127.1, 128.3 138.1, 145.2	1600, 1450

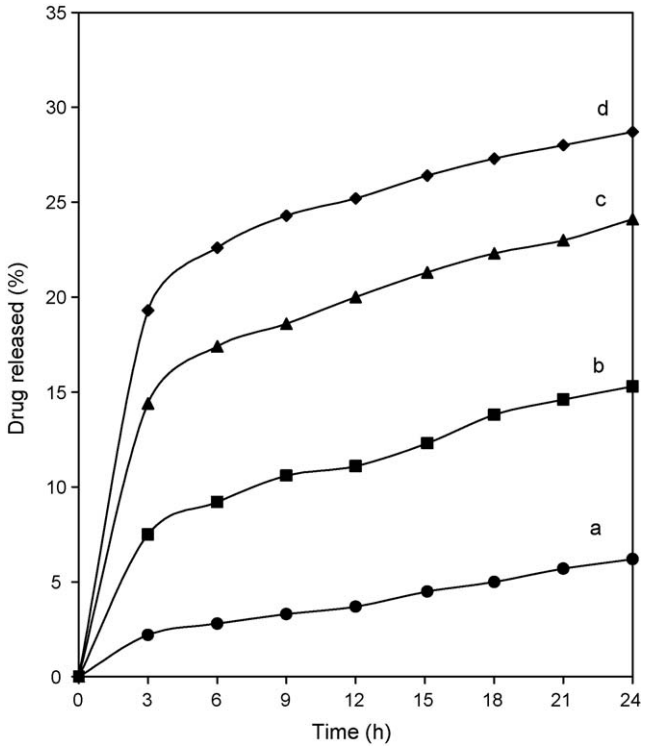


Fig. 1. Percent of released ibuprofen from polymeric carriers as a function of time at HCl buffer (pH 1) and 37 °C. (a) Poly(MOPE-*co*-BMA); (b) poly(MOPE-*co*-HEMA); (c) poly(MOPE-*co*-NVP); (d) poly(MOPE-*co*-MAAm).

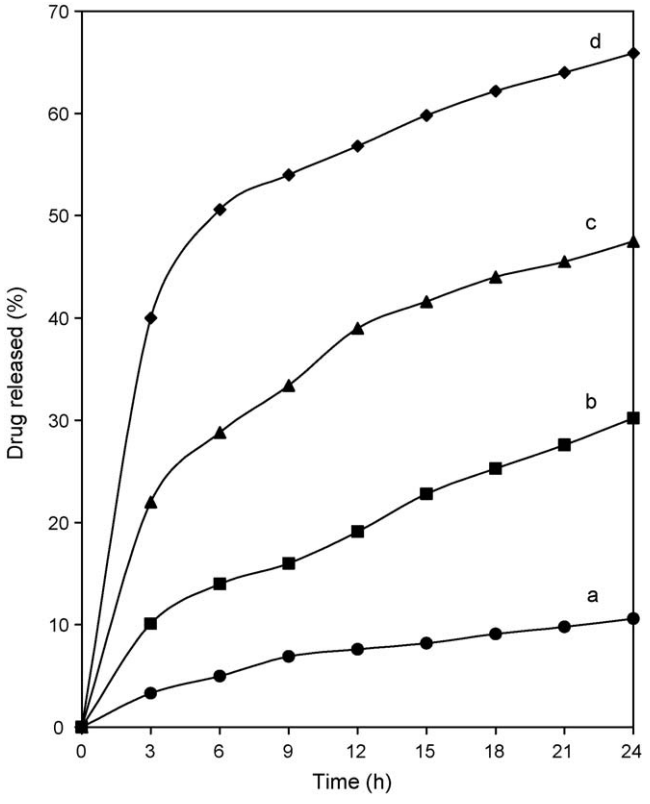


Fig. 2. Percent of released ibuprofen from polymeric carriers as a function of time at phosphate buffer (pH 8) and 37 °C. (a) Poly(MOPE-*co*-BMA); (b) poly(MOPE-*co*-HEMA); (c) poly(MOPE-*co*-NVP); (d) poly(MOPE-*co*-MAAm).

4. Conclusion

In this work, polymeric prodrugs having ibuprofen pendent groups were prepared by the free radical polymerization of new polymerizable acrylic monomer with various comonomers. The structure of polymers was characterized by spectroscopy techniques and their compositions calculated by the ^{1}H NMR spectra data. Study of hydrolysis was carried out similar to the physiological conditions. The results showed that the introduction of hydrophilic units along the polymer chain increases the drug release percentage. As the main purpose of polymeric prodrugs is the achievement of controlled drug release or slow release, application of these polymers as a drug delivery system is expected after in vivo examinations.

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