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# Preparation of acrylic-type derivative of ibuprofen and in vitro evaluation studies of its polymeric prodrugs

Mirzaagha Babazadeh *, Ladan Edjlali, Zeynab Hajizeynalabedini

*Laboratory of Organic Chemistry, Applied Chemistry Department, Faculty of Sciences, Islamic Azad University, Tabriz Branch, Tabriz, Iran*

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## Abstract

Acrylic-type polymeric systems having degradable ester bonds linked to ibuprofen were synthesized and evaluated as materials for drug delivery. Ibuprofen, as a non-steroidal anti-inflammatory drug, was linked to 2-hydroxyethyl methacrylate by activated ester methodology in one-pot procedure. The resulting methacrylic derivative of ibuprofen was copolymerized with 2-hydroxyethyl methacrylate and *n*-butyl acrylate (in 1:3 mole ratio) by free radical polymerization method in *N*,*N*-dimethylformamide solution, utilizing azoisobutyronitrile as initiator at 65-70 $^{o}$C. All of the obtained compounds were characterized by FT-IR, $^{1}$H NMR, $^{13}$C NMR spectroscopy and elemental analysis technique. The average molecular weights of the polymers bearing ibuprofen were determined by gel permeation chromatography and their polydispersity indices resulted in the range of 1.8-1.9. Release studies of ibuprofen were performed into dialysis bags by hydrolysis in buffered solutions (pH 1, 7.4 and 10) at 37 $^{o}$C. Detection of hydrolysis by UV spectroscopy at selected intervals 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 behaviour of polymeric prodrugs is strongly based on the polymer hydrophilicity and the pH value of the hydrolysis solution. The results suggest that these polymeric prodrugs could be useful for release of ibuprofen in controlled release systems.

***Keywords:*** Ibuprofen, Polymeric prodrug, Controlled release system, Polymerization

## 1. Introduction

One field of application that has attracted polymer chemist's attention from the late 1960s onwards is the need for advanced drug delivery systems to improve drug efficacy. Polymer materials were designed and proposed as matrices or depot systems for injectable or implantable systems or devices. One particular approach towards an improved use of drugs for therapeutic applications is the design of polymeric prodrugs or polymer–drug conjugates [1-4]. Polymeric prodrug is a conjugation of a drug with a polymer, which has several advantages. The main advantages include: (a) an increase in water solubility of low soluble or insoluble drugs, and therefore, enhancement of drug bioavailability; (b) protection of drug from deactivation and preservation of its activity during circulation, transport to targeted organ or tissue and intracellular trafficking; (c) an improvement in pharmacokinetics; (d) a reduction in antigenic

* Corresponding author. Tel.: +98 4113318681; fax: +98 4113318687
*E-mail address:* ma_babazadeh@yahoo.com (M. Babazadeh)

activity of the drug leading to a less pronounced immunological body response; (e) the ability to provide passive or active targeting of the drug specifically to the site of its action; (f) the possibility to form an advanced complex drug delivery system, which, in addition to drug and polymer carrier, may include several other active components that enhance the specific activity of the main drug. Due to these advantages over to free form of a drug, the polymeric prodrug conjugates has lead into a new era of drug delivery systems [5-8].

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 mucous and by their frequent poor water solubility [9]. 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 [10].
Ibuprofen, 2-(4-isobutylphenyl)propionic acid is a member of the NSAID's which is used as an inhibitor of prostaglandin synthetase in body. It is effective in the long-term management of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and acute gout, as well as mild to moderate pain and dysmenorrhea. Its gastrointestinal side effects (such as dyspepsia, gastrointestinal bleeding, and even perforation), renal side effects and some additional side effects (such as hypersensitivity reactions and distinct salicylate intoxication) limit the use of ibuprofen [11-12].

In recent years, some NSAIDs such as ibuprofen [13-18], indomethacin [15, 19], naproxen [12, 20], ketoprofen [12, 13, 20] and diclofenac [7, 20, 21] have been chemically attached to various polymer backbones and their hydrolytic behaviors studied. This present work develops an efficient chemical method to design and synthesis of acrylic type polymeric carriers for release of ibuprofen in controlled release systems. 2-[(4-Isobutylphenyl)propionyloxy]ethyl methacrylate (MEI), as an acrylic type polymerizable derivative of ibuprofen was synthesized by esterification methodology. The obtained MEI was then copolymerized with 2-hydroxyethyl methacrylate (HEMA) or *n*-butyl acrylate (BA) by free radical polymerization technique. The release of ibuprofen from the obtained polymeric prodrugs was carried out *in vitro* by hydrolysis in buffered solutions at various pH values and the quantity of the released drug detected by UV spectroscopy. The effects of neighboring groups and pH values on release of ibuprofen are discussed.

## 2. Experimental

### *2.1. Material*

Ibuprofen was purchased from Aldrich chemical company. *N,N*-Dicyclohexylcarbodiimide (DCC), dimethylamino pyridine (DMPA), HEMA and BA were obtained from Merck chemical company. Azoisobutyronitrile (AIBN) was obtained from Fluka chemical company and recrystallized from methanol. *N,N*-Dimethylformamide (DMF) was dried over anhydrous $MgSO_4$ for two days and distilled under reduced pressure. All other chemicals were reagent grade or purer.

### 2.2. *Instrumental measurements*

FT-IR spectra were recorded by use of KBr pellets on a Shimadzu 4300 spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker 400 MHz spectrometer in $CDCl_3$ or DMSO-$d_6$ solution. The amount of released ibuprofen was determined by a 2100 Shimadzu UV spectrophotometer at the adsorption maximum of the free drug in aqueous buffered solutions ($\lambda_{max}$=264 nm) using a 1-cm quartz cell. Molecular weights of polymers were determined with a

Maxima 820 gel permeation chromatography (GPC) unit. (Mobile phase, DMF; run time, 50 min; column temperature, 50 $^{o}$C). Well-characterized polyethylene oxide was used in the calibration within the range of $M_w$ between "2600–885000". Elemental analyses were carried out with a Heareus CHN-ORAPID instrument.

### *2.3. Preparation of 2-[(4-Isobutylphenyl)propionyloxy]ethyl methacrylate (MEI)*

In a two-necked flask, 4.1 g (20 mmol) of ibuprofen and 0.25 g (2 mmol) of DMAP were dissolved in 50 ml of DMF. The flask was cooled until -20 °C and a solution of 4.1 g (20 mmol) of DCC dissolved in 40 ml of DMF was added dropwise into flask solution at this temperature. Then, 2.6 g (20 mmol) of HEMA was dissolved in 15 ml of DMF and added to the flask mixture at the mentioned temperature. The reaction mixture was vigorously stirred at -20 °C for 1 h and returned slowly to room temperature. The mixture was stirred at room temperature about 24 h and filtered for remove of white precipitation of *N,N*-dicyclohexylurea (DCU). Then, DMF was evaporated in vacuum and the obtained solid recrystallized from methanol to give 5.0 g (78%) of MEI.

FT-IR (KBr, cm$^{-1}$) 3065 (C-H aromatic), 3030 (C-H vinylic), 2950, 2890 (C-H aliphatic), 1710, 1735 (C=O ester), 1637 (C=C vinylic), 1600, 1480 (C=C aromatic).

$^{1}$H NMR ($CDCl_3$, ppm) 0.9 (d, 6H, -CH($C\underline{H}_3$)$_2$), 1.5 (d, 3H, -ArCH$C\underline{H}_3$), 1.9 (m, 1H, -$C\underline{H}Me_2$), 2.1 (s, 3H, =$CC\underline{H}_3$), 2.5 (d, 2H, Ar-$C\underline{H}_2$-), 3.7 (q,1H, Ar-$C\underline{H}$-), 4.2 (t, 2H, -$C\underline{H}_2$OCOCH-), 4.5 (t, 2H, -$C\underline{H}_2$OCOC=), 5.2 (d, 1H, $CH_2$=C), 6.0 (d, 1H, $CH_2$=C), 7.1-7.4 (q, 4H, aryl-$\underline{H}$).

$^{13}$C NMR ($CDCl_3$, ppm) 21 (2C, -CH($\underline{C}H_3$)$_2$), 22 (1C, -$\underline{C}HMe_2$), 30 (1C, =C($\underline{C}H_3$)), 45 (1C, Ar-$\underline{C}H_2$-), 50 (1C, Ar-$\underline{C}$H-), 61, 62 (2C, -$\underline{C}H_2$OOC-), 125 (1C, $\underline{C}H_2$=C), 141 (1C, $CH_2$=$\underline{C}$), 126, 129, 140, 154 (6C, aromatic carbons), 169, 172 (2C, ester carbons).

Elemental analysis for $C_{19}H_{26}O_4$ (318 gmol$^{-1}$), calculated: C 71.69, H 8.11; found: C 71.72, H 8.25%.

### *2.4. Copolymerization of MEI with acrylic monomers*

In two Pyrex glass ampoules, a mixture of 3.18 g (10 mmol) of MEI, 0.16 g (1 mmol) of AIBN, 3.95 g (30 mmol) of HEMA or 3.84 g (30 mmol) of BA was dissolved in 12 ml of dried DMF, respectively. The ampoules were then degassed, sealed under vacuum, maintained at 65-70 ºC in a water bath and shaken by a shaker machine for about 30 h. After this time, the viscous solutions were separately poured from the ampoules into 150 ml of cooled methanol as non-solvent. The precipitates were collected, washed with non-solvent for several times and dried under vacuum at room temperature. The yields of polymers are given in Table 1.

### *2.5. Method of hydrolysis*

The polymer-drug conjugates were dried under vacuum at room temperature and sieved with a 200-mesh sieve. Each of dried polymer-drug conjugates (200 mg) was poured into 5 ml of aqueous buffered solution (pH 1, 7.4 and 10) at 37 ºC and 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 ºC. 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.

### *2.6. Characterization of hydrolysis products*

Twenty milligram of the polymer-drug conjugate was dispersed into 20 ml of buffered solution (pH 10) and maintained at 37 °C. After 24 h, the hydrolysis solution was sampled, neutralized with 1 N 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 and showed that the hydrolysis product is ibuprofen.

## 3. Results and discussion

### *3.1. Synthetic route for preparation of MEI*

Two different synthetic methods have been reported in the preparation of polymers that contain pendent drug substituents. In first method, the drug is converted to a polymerizable monomer by consecutive aminolysis or transesterification procedure, and then polymerized or copolymerized with a wide range of suitable monomers to produce polymer-drug combinations. This method covers a wide range of nucleophiles such as primary, secondary and aromatic amines and alcohols. In other method, the drug agent is attached to preformed polymer backbones *via* degradable chemical bonds to produce polymeric prodrugs [22-24]. MEI was easily prepared by direct esterification of ibuprofen with HEMA in the presence of DCC in DMF solution (Fig. 1).

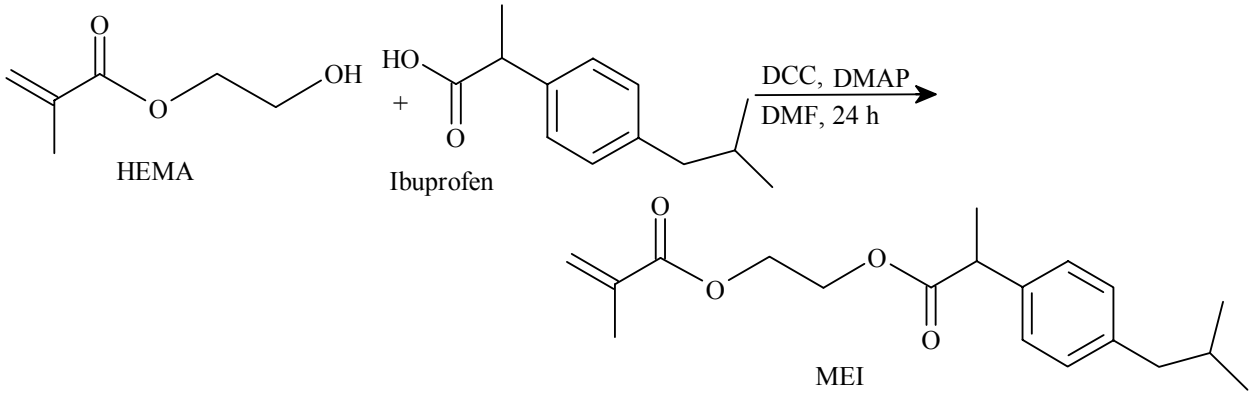



**Fig. 1** The synthesis route of acrylic type derivative of ibuprofen (MEI)

The hydroxyl group of HEMA reacted with carboxyl group of ibuprofen and the resulted water was absorbed by DCC to produce DCU as a white precipitate. After completing of reaction, the white precipitate was separated and the solvent was evaporated to give MEI as stable monomer. The resultant FT-IR, $^{1}$H NMR, $^{13}$C NMR spectra and elemental analysis data confirmed the structure of MEI and its purity. The related $^{1}$H and $^{13}$C NMR spectra of MEI are shown in Figs. 2 and 3, respectively.

### *3.2. Synthesis and characterization of polymeric prodrugs*

Drug-containing monomer, MEI, was easily copolymerized with HEMA and BA in dried DMF solution, by free radical technique at 65-70 °C using AIBN as initiator (Fig. 4). The resulted copolymers were colorless, amorphous and soluble in DMSO and DMF, but insoluble in water and alcohols. The conversions of monomers to the related copolymers were determined gravimetrically after exhaustive drying of the isolated copolymer samples. The preparation conditions and yields of copolymers are shown in Table 1.

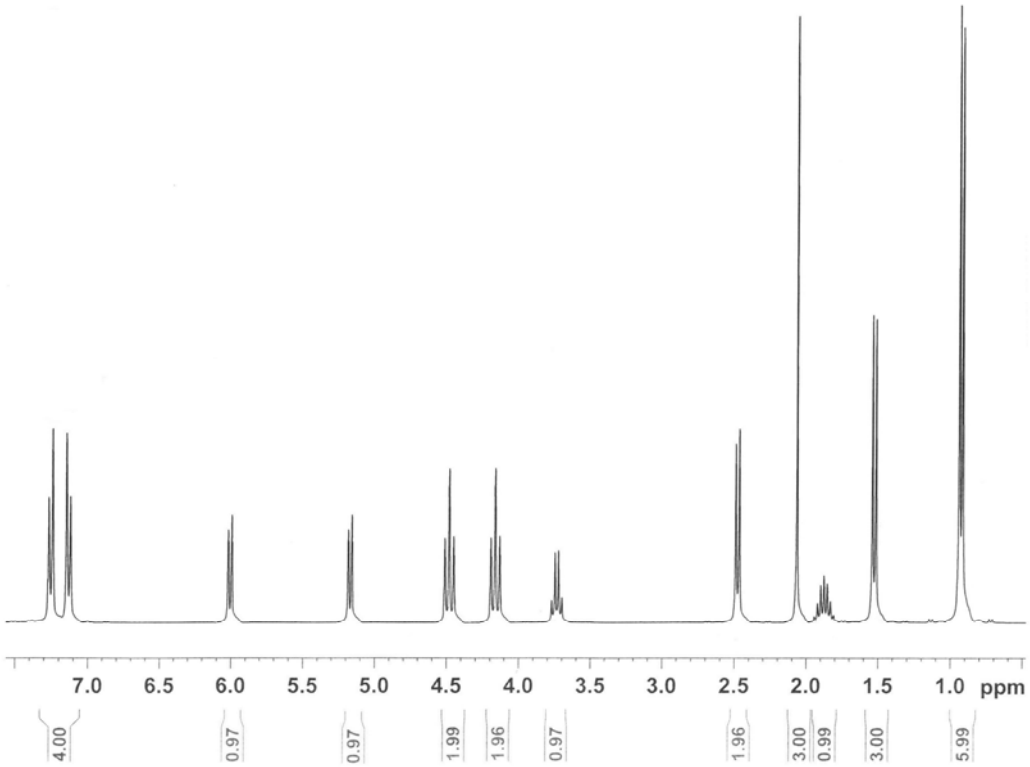



**Fig. 2** $^{1}$H NMR spectrum of MEI in $CDCl_3$

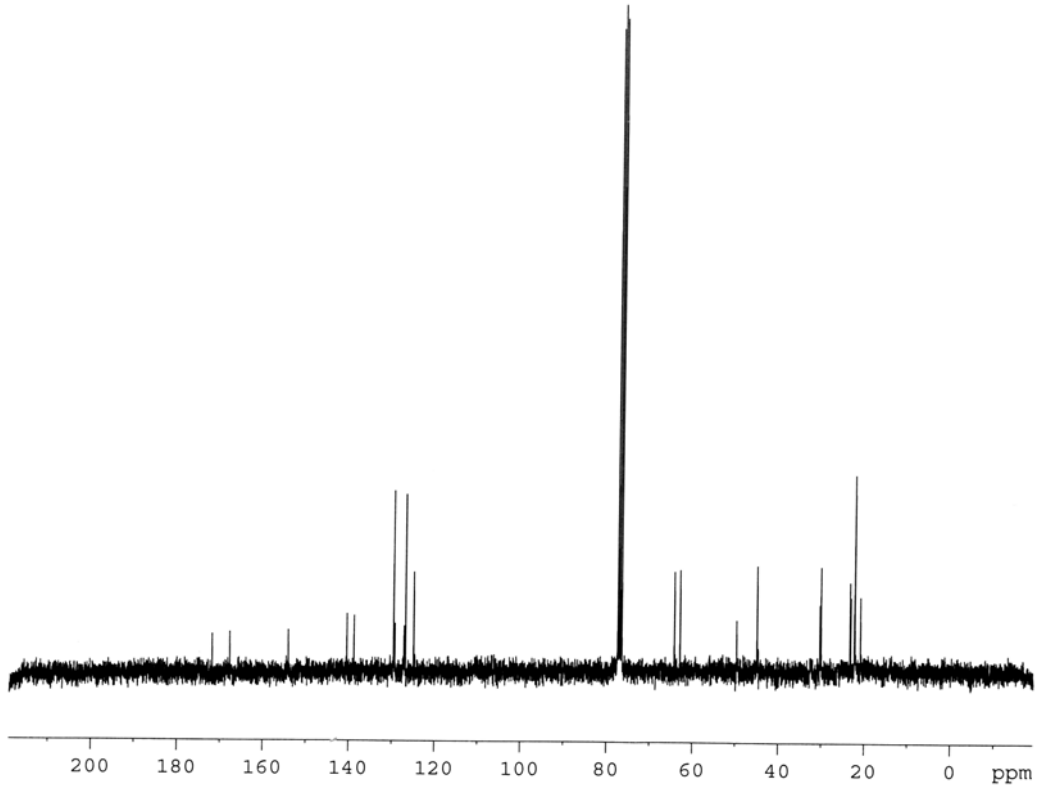
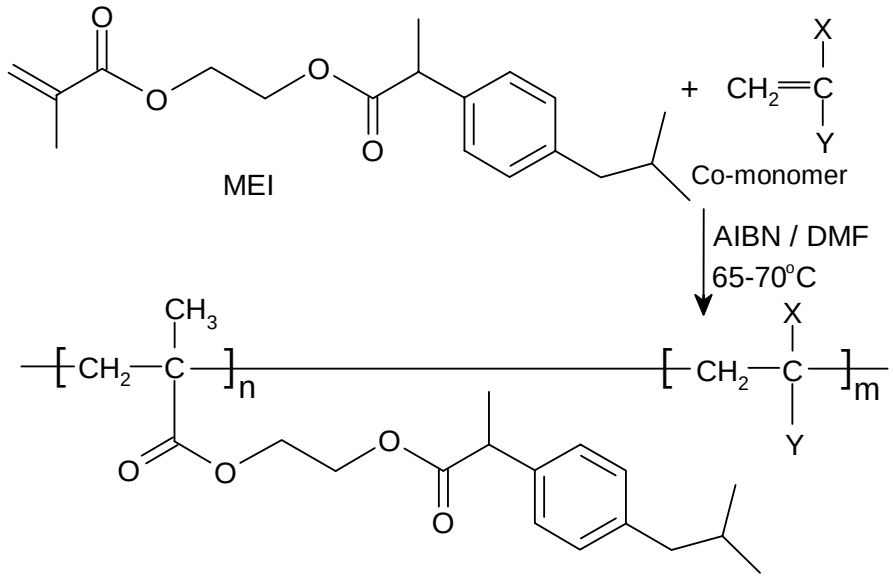



**Fig. 3** $^{13}$C NMR spectrum of MEI in $CDCl_3$

**Table 1**
The preparation conditions and yields of the polymeric prodrugs

| Sample | $[M_1]$ (mmol $L^{-1}$) | $[M_2]$ (mmol $L^{-1}$) | Non-solvent | Yield (%) |
|---|---|---|---|---|
| Poly(MEI-*co*-HEMA) | MEI (10) | HEMA (30) | Methanol | 63.5 |
| Poly(MEI-*co*-BA) | MEI (10) | BA (30) | Methanol | 69.5 |




**Poly(MEI-*co*-HEMA):** X=Me, Y=$COOCH_2CH_2OH$
**Poly(MEI-*co*-BA):** X=H, Y=$COOCH_2CH_2CH_2CH_3$

**Fig. 4** Copolymerization of MEI with HEMA or BA to give polymeric prodrugs

The prepared prodrugs were characterized through a variety of techniques including FT-IR, $^1H$ and $^{13}C$ NMR spectroscopy. The results confirmed the structure of the synthesized polymers. Spectral characteristics of functional groups of copolymers having ibuprofen substituents are given in Table 2. One parameter in characterization of polymeric prodrugs is determination of molecular weight distribution and the average molecular weights. The weight and number-average molecular weights of the synthesized polymeric prodrugs were estimated by GPC instrument. The obtained values are shown in Table 3.

**Table 2**
Spectral characterization of the polymeric prodrugs

| Sample | Functional group | $^1H$ NMR (ppm) | $^{13}C$ NMR (ppm) | FT-IR ($cm^{-1}$) |
|---|---|---|---|---|
| Poly(MEI-*co*-HEMA) | COO | - | 175, 169 | 1735 |
| | OH | 5.5 | - | 4200-3200 |
| Poly(MEI-*co*-BA) | COO | - | 176, 171 | 1735 |
| All polymers | $CH_2O$ | 4.2 | 63 | 1100 |
| | Ph | 7.0-8.0 | 126, 129, 140, 154, | 1600, 1450 |

**Table 3**
Elemental analyses, molecular weights and mole compositions of polymers

| Sample | C (%) | H (%) | $M_n$ ($\times 10^{-3}$) | $M_w/M_n$ | n (%) | m (%) |
|---|---|---|---|---|---|---|
| Poly(MEI-*co*-HEMA) | 64.7 | 7.9 | 11.3 | 1.9 | 33 | 66 |
| Poly(MEI-*co*-BA) | 68.5 | 8.8 | 15.7 | 1.8 | 27 | 73 |

$^1$H NMR spectroscopic analysis and elemental analysis data are powerful tools for the determination of copolymer compositions because of their simplicity, rapidity and sensitivity [25, 26]. Therefore, copolymer compositions were determined from $^1$H NMR spectroscopic data and elemental analysis of prodrugs. The calculated compositions of polymeric prodrugs are presented in Table 3. The results obtained from $^1$H NMR data and elemental analyses were relatively in good agreement.

*3.3. 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 [2]. The *in vitro* hydrolysis behavior of polymeric prodrugs was studied in physiological conditions (aqueous phosphate or hydrochloric acid buffers, at 37 $^o$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 was determined by a UV spectrophotometer.

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 methylene group is hydrolyzed during the reaction time. 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 methylene group does not undergo hydrolysis under mild conditions. This can be related to the steric hindrance of bulk polymer chains, which decrease the bond mobility [27]. Figs. 5-7 show the release of ibuprofen from polymeric prodrugs as a function of time under mild conditions in HCl buffer (pH 1) and $KH_2PO_4$-$Na_2HPO_4$ buffer (pH 7.4 and 10). The order of hydrolysis is: Poly(MEI-*co*-HEMA)>Poly(MEI-*co*-BA).

As shown in Figs. 5-7, the release rate of ibuprofen from polymeric prodrugs at alkaline medium was higher than the release rate of drug in acidic condition. It seems that polymeric prodrugs have a low degree of swelling in the acidic medium and the drug is protected against hydrolysis. The degree of hydrolysis increases as the polymer passes from acidic to alkali medium. In alkali pH, the polymers have reached a degree of swelling that makes the labile bonds accessible to hydrolysis. The hydrolysis mechanism of polymeric prodrugs in various pH medias is shown in Fig. 8.

Different factors such as solubility of polymers and neighbouring effect of side groups can affect the overall rate of hydrolysis. The hydrophilic copolymer containing ibuprofen was hydrolyzed in buffer solutions rather than hydrophobic copolymer. As shown in Figs. 5-7, poly(MEI-*co*-HEMA) was rapidly hydrolyzed because of higher hydrophilicity of HEMA units and poly(MOPE-*co*-BA) was slowly hydrolyzed because of hydrophobicity of BA units in the copolymer structure.

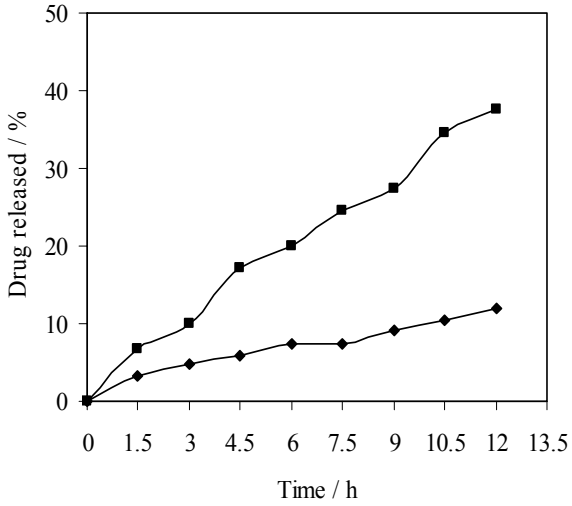



**Fig. 5** Percent of released ibuprofen from polymeric carriers as a function of time at hydrochloric acid buffer (pH 1) and 37 $^{o}$C. ♦ Poly(MEI-*co*-BA); ■ Poly(MEI-*co*-HEMA)

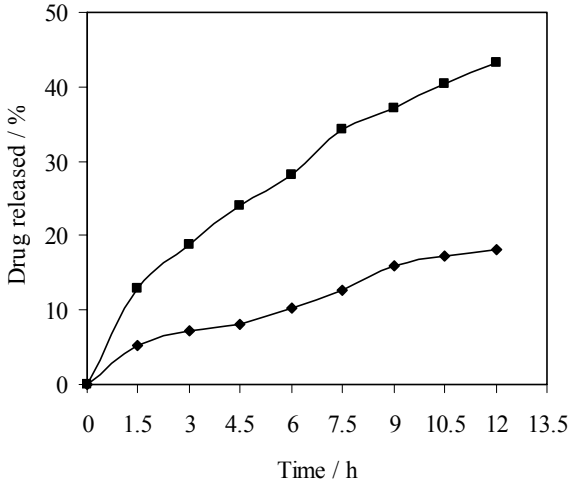



**Fig. 6** Percent of released ibuprofen from polymeric carriers as a function of time at phosphate buffer (pH 7.4) and 37 $^{o}$C. ♦ Poly(MEI-*co*-BA); ■ Poly(MEI-*co*-HEMA)

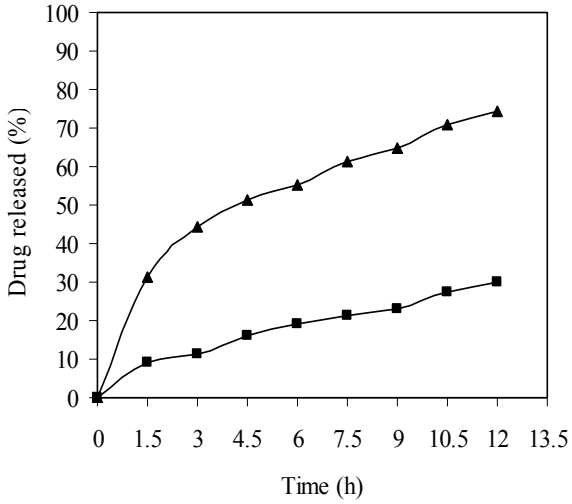



**Fig. 7** Percent of released ibuprofen from polymeric carriers as a function of time at phosphate buffer (pH 10) and 37 oC. ■ Poly(MEI-co-BA); ▲ Poly(MEI-co-HEMA)

The results show that with passing polymeric prodrugs from acidic media to slightly alkaline pH, the labile bonds are better accessible to hydrolysis. Therefore, in alkaline pH value, the polymers are easily degraded to release of ibuprofen.

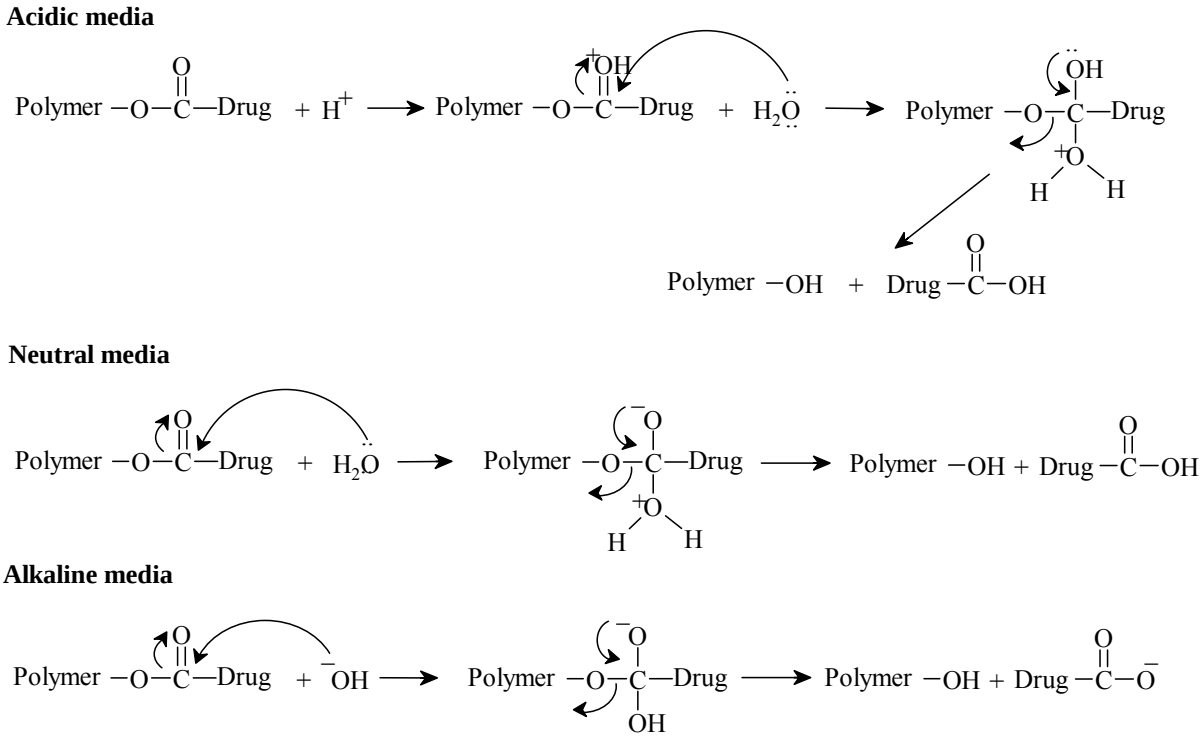



**Fig. 8** The hydrolysis mechanism of polymeric prodrugs in different pH media

## 4. Conclusion

In this work, MEI as an acrylic type polymerizable derivative of ibuprofen was synthesized from reaction between HEMA and ibuprofen by esterification method. Then, the polymeric prodrugs containing ibuprofen pendent groups were synthesized by the free radical polymerization of MEI with acrylic monomers such as HEMA or BA. The structure of the synthesized MEI and polymeric prodrugs were characterized by various spectroscopy techniques. Hydrolysis of polymeric prodrugs was carried out similar to the physiological conditions and the results showed that the introduction of hydrophilic units along the polymer chain improves the hydrolytic behaviour. Also, the resultant release profiles of drug from prodrugs showed that the synthesized polymeric prodrugs were pH-sensitive polymers. Therefore, the studied polymers in the present investigation can be used in prolongation of transit time and are useful as drug carriers for development of pH-sensitive polymeric prodrugs. 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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