



## Vinyl Ester Polymers Containing Ibuprofen Pendant Groups: Synthesis, Characterization, and Evaluation

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### ABSTRACT

Vinyl ester polymeric systems linked to ibuprofen were synthesized and evaluated as materials for drug delivery. The carboxyl group of ibuprofen was converted into vinyl ester group by reacting ibuprofen with vinyl acetate in the presence of mercuric acetate as a catalyst. The resultant ibuprofen derivative of vinyl ester was then copolymerized with 2-hydroxyethyl methacrylate or methyl methacrylate (in 1:3 mole ratios) by utilizing azoisobutyronitrile as an initiator at the temperature range of 65-70°C. The structure of all compounds was characterized and confirmed by FTIR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR spectroscopy techniques and elemental analysis. Gel permeation chromatography was used for determination of the average molecular weights and polydispersity indices of the ibuprofen containing polymers. The hydrolysis of drug-polymer conjugates was carried out in cellophane membrane dialysis bags containing aqueous buffer solutions (pH 1, 7.4, and 10) at 37°C for 48 h. Detection of hydrolysis solutions by UV-vis spectroscopy at selected intervals showed that the drug could be released by hydrolysis of the ester bonds which were formed between the drug and polymer backbone. The release profiles indicated that the hydrolytic behaviour of polymeric prodrugs is strongly based on polymer hydrophilicity and pH of the hydrolysis solution. The results suggest that these prepared polymeric prodrugs could be useful for release of ibuprofen in controlled release systems.

### Key Words:

ibuprofen;  
non-steroidal anti-inflammatory  
drugs;  
polymeric prodrugs;  
controlled release systems;  
polymerization.

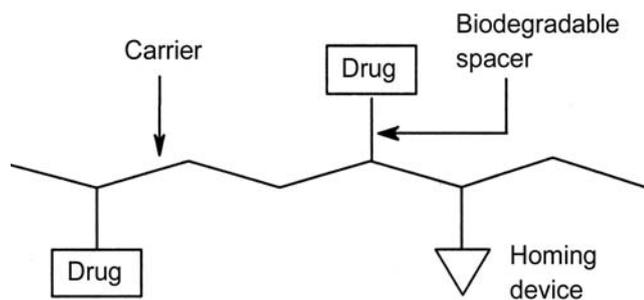
### INTRODUCTION

The design and application of "polymeric prodrugs" are interesting fields that are expanded and developed continuously because of the intrinsic advantages offered by specific macromolecular systems in new and risk therapies [1-4]. Polymeric prodrug, as a conjugation of a drug with a polymer, has many advantages such as increased drug solubility, prolonged drug release, increased stability, and decreased toxicity [5,6].

For the first time in 1975, Prof. Ringsdorf proposed a rational model for pharmacologically active polymers [7]. This proposed model consisted mainly of five components: the polymeric backbone, the drug, the spacer, the targeting group, and the solubilizing agent (Figure 1). Although oversimplified, this model is still considered a significant mark in the history of polymeric prodrug design.

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**Figure 1.** The proposed model by Ringsdorf for pharmacologically active polymers.

The polymeric carrier can be either an inert or a biodegradable polymer. The drug can be fixed directly or via a spacer group onto the polymer backbone. The proper selection of this spacer opens the possibility of controlling the site and the release rate of active drug from the conjugate by hydrolytic or enzymatic cleavage [8].

The therapeutic use of non-steroidal anti-inflammatory drugs (NSAIDs) is often restricted by the necessity to deliver the drug to the 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 NSAIDs which is used as an inhibitor of the 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 (e.g., dyspepsia, gastrointestinal bleeding, and even perforation), renal, and some additional side effects (e.g., hypersensitivity reactions and distinct salicylate intoxication) limit the use of ibuprofen [11,12].

In recent years, the polymeric prodrugs of some NSAIDs such as ibuprofen [13-17], indomethacin

[18,19], naproxen [20,21], ketoprofen [12,14] and diclofenac [22,23] in which the drug is attached covalently to polymer backbone have been developed and studied.

This research work describes an efficient chemical method to design and in vitro evaluation of new vinyl ester type polymeric prodrugs of ibuprofen as materials for drug delivery systems. Vinyl 2-(4-isobutylphenyl) propionate (VIP), as a new vinyl ester derivative of ibuprofen was first synthesized by reacting ibuprofen and vinyl acetate in the presence of mercuric acetate as a catalyst. The obtained VIP was then copolymerized with 2-hydroxyethyl methacrylate (HEMA) or methyl methacrylate (MMA) by free radical polymerization method to give polymeric prodrugs. The release of ibuprofen from the synthesized polymeric prodrugs was carried out in vitro by hydrolysis of prodrugs in buffered solutions at various pH values and the quantity of the released drug was detected by UV-vis spectroscopy. The effects of neighbouring groups and pH values on release of ibuprofen are reported and discussed as well.

## EXPERIMENTAL

### Materials

Ibuprofen was purchased from Aldrich. Mercuric acetate, vinyl acetate, sodium acetate, HEMA and MMA were obtained from Merck and used as received. Azobisisobutyronitrile (AIBN) was obtained from Fluka 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 grades or purer.

### Instrumental Measurements

FTIR spectra were recorded on a Shimadzu 4300 spectrophotometer.  $^1H$  and  $^{13}C$  NMR spectra were recorded on Bruker 300 MHz spectrometer in  $CDCl_3$  or  $DMSO-d_6$  solution. The amount of the released ibuprofen was determined by a 2100 Shimadzu UV-vis spectrophotometer at the maximum adsorption 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, and column temperature: 50°C). Well-characterized polyethylene oxide was used in the calibration within the range of  $\overline{M}_w$  between 2600 and 885000 g/mol. Elemental analyses were carried out with a Heareus CHN-ORAPID instrument.

### Preparation of Vinyl 2-(4-isobutylphenyl)propionate (VIP)

An amount of 2.6 g (12.6 mmol) of ibuprofen and 0.3 g of mercuric acetate were dissolved in 30 mL of vinyl acetate and stirred for 30 min at room temperature. Then, 0.2 mL of concentrated sulphuric acid was added into the solution and refluxed for about 3 h. The solution was then cooled to room temperature and 1.0 g of sodium acetate was added to quench the catalyst. The solution was filtered, concentrated and the crude product was then purified by silica gel column chromatography by eluting with petroleum ether/ethyl acetate (30:1, v/v) to give 2.5 g (85%) of VIP.

FTIR (KBr,  $\text{cm}^{-1}$ ),  $\nu$ : 3050 (C-H aromatic and vinylic), 2890 (C-H aliphatic), 1740 (C=O ester), and 1600 and 1480 (C=C).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , ppm),  $\delta$ : 0.9 (d, 6H,  $-\text{CH}(\text{CH}_3)_2$ ), 1.5 (d, 3H,  $-\text{ArCHCH}_3$ ), 1.9 (m,  $^1\text{H}$ ,  $-\text{CHMe}_2$ ), 2.5 (d, 2H,  $\text{Ar-CH}_2-$ ), 3.7 (q, 1H,  $\text{Ar-CH-}$ ), 4.5 (d, 1H,  $\text{CH}_2=\text{C}$ ), 4.9 (d, 1H,  $\text{CH}_2=\text{C}$ ), 7.0-7.3 (q, 4H, aryl-H), and 7.4 (q, 1H,  $\text{CH}_2=\text{CH}$ ).

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm),  $\delta$ : 20 (1C,  $-\text{CH-CH}_3$ ), 21 (2C,  $-\text{CH}(\text{CH}_3)_2$ ), 22 (1C,  $-\text{CHMe}_2$ ), 30 (1C,  $\text{Ar-CH}_2-$ ), 45 (1C,  $-\text{CH-CH}_3$ ), 125 (1C,  $\text{CH}_2=\text{CH-}$ ), 155 (1C,  $\text{CH}_2=\text{CH-}$ ), 126, 129, 138, and 140 (6C, aromatic carbons), and 172 (1C, C=O).

Elemental analysis for  $\text{C}_{15}\text{H}_{20}\text{O}_2$  (232.32  $\text{gmol}^{-1}$ ), calculated: C = 77.58 and H = 8.62%; found: C = 77.25 and H = 8.43%.

### Copolymerization of VIP with Methacrylic Monomers

In two Pyrex glass ampoules, the mixtures of 2.32 g

(10 mmol) of VIP, 0.16 g (1 mmol) of AIBN, 3.95 g (30 mmol) of HEMA and/or 3.0 g (30 mmol) of MMA were dissolved in 15 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 30 h. After that, the obtained viscous solutions were separately poured into 150 mL of cold 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 the resultant polymers are given in Table 1.

### Method of Hydrolysis

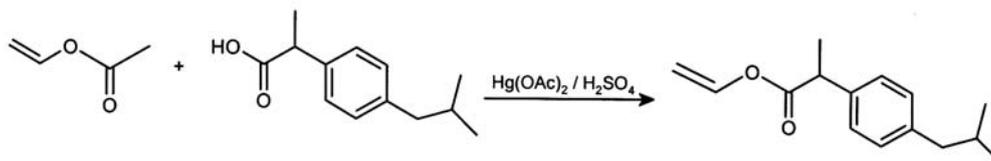
The polymer-drug conjugates were dried under vacuum at room temperature and sieved with a 200-mesh sieve. Each dried polymer-drug conjugate (20 mg) was transferred into a 5 mL of aqueous buffered solution with respective pH 1, 7.4, and 10 at 37°C and each mixture was directed into a cellophane membrane dialysis bag. The bag was closed and transferred into a flask containing 25 mL of the same buffer solution maintained at 37°C. The external solution was continuously stirred and a 3-mL sample was removed at selected intervals and each time it was replaced by 3 mL of buffer solution. The quantity of released drug was analyzed by means of an UV-vis spectrophotometer and determined from the calibration curve obtained under the same conditions prior to test samples [3,13-15].

### 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 48 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

**Table 1.** Preparation conditions and yields of the polymeric prodrugs.

Sample	[M <sub>1</sub> ] (mmol/L)	[M <sub>2</sub> ] (mmol/L)	Non-solvent	Yield (%)
Poly(VIP-co-HEMA)	VIP (10)	HEMA (30)	Methanol	75.2
Poly(VIP-co-MMA)	VIP (10)	MMA (30)	Methanol	78.7



**Scheme I.** The synthesis route of vinyl ester type derivative of ibuprofen (VIP).

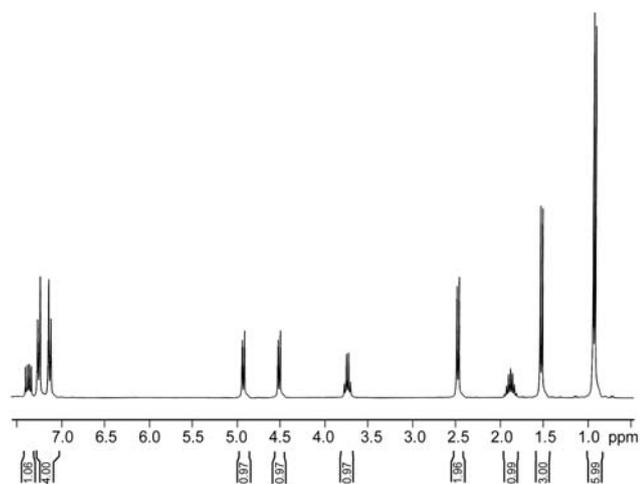
residue was characterized by melting point measurement and IR spectroscopy which showed that the hydrolysis product was ibuprofen.

## RESULTS AND DISCUSSION

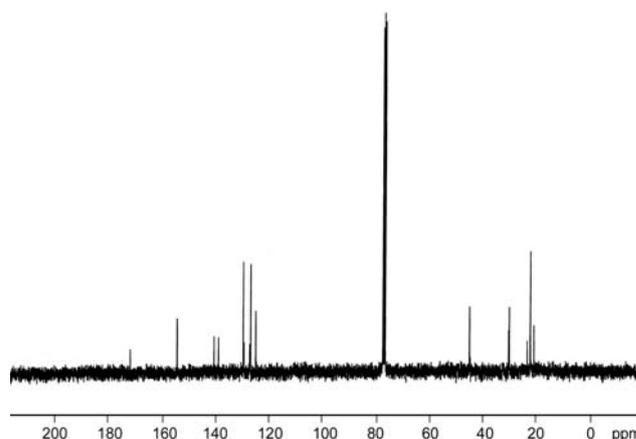
### Synthetic Route for Preparation of VIP

Vinyl acetate has been used as acylating agent in many successful resolution of alcohol. Since the alcohols freed from the reaction tautomerize rapidly to volatile acetaldehyde, making the process irreversible and simple for product isolation [24]. Yang et al. [25] and Cai et al. [26] have already reported a method for conversion of carboxylic acids to the corresponding vinyl ester derivatives by using vinyl acetate.

In the present work, ibuprofen reacted with vinyl acetate in the presence of mercuric acetate as a catalyst and the obtained corresponding vinyl ester (VIP) was collected in high yield after purification by column chromatography (Scheme I). The resultant FTIR,  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR spectra and elemental analysis data confirmed the structure of VIP and its purity. The related  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of VIP are shown in Figures 2 and 3, respectively.



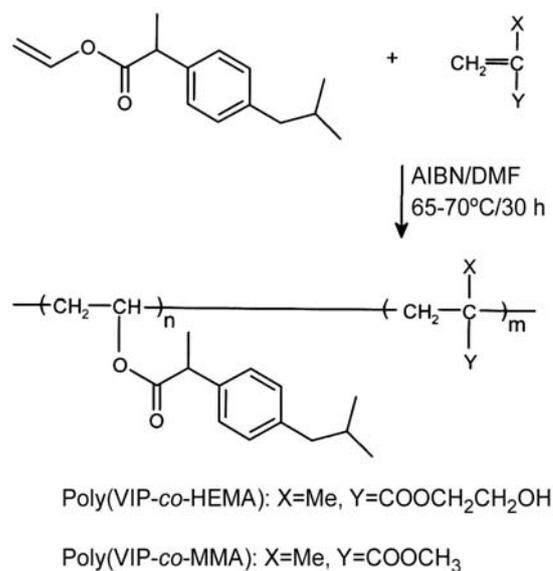
**Figure 2.**  $^1\text{H}$  NMR spectrum of VIP in  $\text{CDCl}_3$ .



**Figure 3.**  $^{13}\text{C}$  NMR spectrum of VIP in  $\text{CDCl}_3$ .

### Synthesis and Characterization of Polymeric Prodrugs

Drug-containing monomer, i.e., VIP was easily copolymerized with HEMA and MMA in dried DMF solution, by free radical mechanism at the temperature range of 65-70°C by using AIBN as initiator



**Scheme II.** Copolymerization of VIP with HEMA or MMA to give polymeric prodrugs.

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

Sample	Functional group	<sup>1</sup> H NMR (ppm)	<sup>13</sup> C NMR (ppm)	FTIR (cm <sup>-1</sup> )
Poly(VIP-co-HEMA)	-COO-	-	173, 170	1735
	-OH	5.5	-	4200-3200
Poly(VIP-co-MMA)	-COO-	-	175, 171	1735
	-OCH <sub>3</sub>	3.8	61	1100
All polymers	Ph	7.0-8.0	126, 129 135, 140	1600, 1480

(Scheme II). The resulted copolymers were colourless, amorphous and soluble in DMSO and DMF, but insoluble in water and alcohols. The conversions of monomers to the corresponding copolymers were determined gravimetrically after exhaustive drying of the isolated copolymer samples. The preparation conditions and yields of copolymers are shown in Table 1. Characterization of the prepared prodrugs through a variety of techniques including FTIR, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopies confirmed their structures. 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 hence the average molecular weights. The molecular weights of the synthesized polymeric prodrugs were estimated by GPC technique and are shown in Table 3. Also, the mole composition of polymeric prodrugs was determined from the related elemental analyses data which are presented in Table 3.

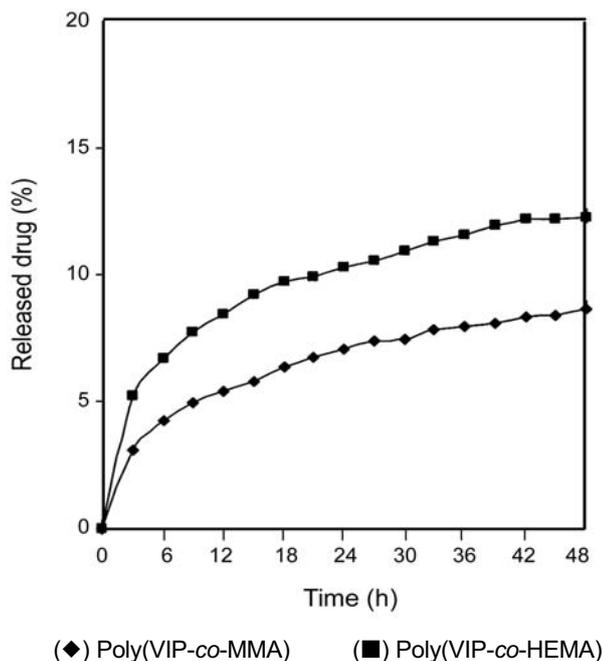
### Drug Release by Hydrolysis of Polymeric Prodrugs

It has been widely believed 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. In this work, the in vitro hydrolytic behaviour of polymeric prodrugs 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 its quantity was determined by a UV-vis spectrophotometer. Detection of the hydrolyzing solution by UV-vis spectrophotometer showed that the hydrolysis rate of the synthesized polymers is lower than acrylic-type and vinyl ether-type polymeric prodrugs of ibuprofen which have been reported, previously [13,14]. This can be related to direct linkage of drug to polymer backbone in which steric hindrance of bulk polymer chain decreases the bond mobility between drug and polymer. Previous research works have demonstrated that introduction of spacer groups between the backbone

**Table 3.** Elemental analyses, molecular weights, and mole compositions of polymeric prodrugs.

Sample	C (%)	H (%)	M <sub>n</sub>	M <sub>w</sub> /M <sub>n</sub>	VIP (%)	HEMA (%)	MMA (%)
Poly(VIP-co-HEMA)	64.72	8.08	18620	1.9	29	71	-
Poly(VIP-co-MMA)	67.66	8.27	15510	1.9	25	-	75



**Figure 4.** Percentage of released ibuprofen from polymeric carriers as a function of time at hydrochloric acid buffer (pH 1) and 37°C.

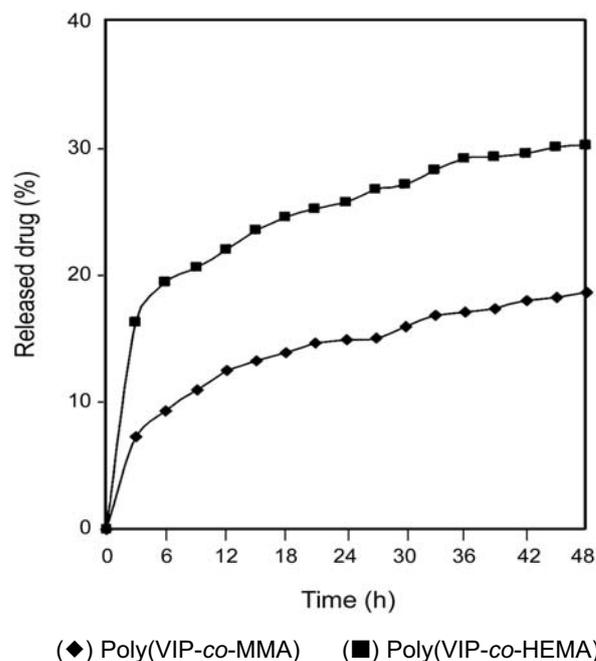
of the polymer and drug or hydrophilic units along the polymer chain improve the hydrolysis behaviour of polymers [9,13,14].

Figures 4-6 show the release of ibuprofen from polymeric prodrugs as a function of time under mild conditions in HCl buffer (pH 1) and  $\text{KH}_2\text{PO}_4\text{-Na}_2\text{HPO}_4$  buffers (pH 7.4 and 10), respectively. The order of hydrolysis is:

$$\text{poly(VIP-co-HEMA)} > \text{poly(VIP-co-MMA)}$$

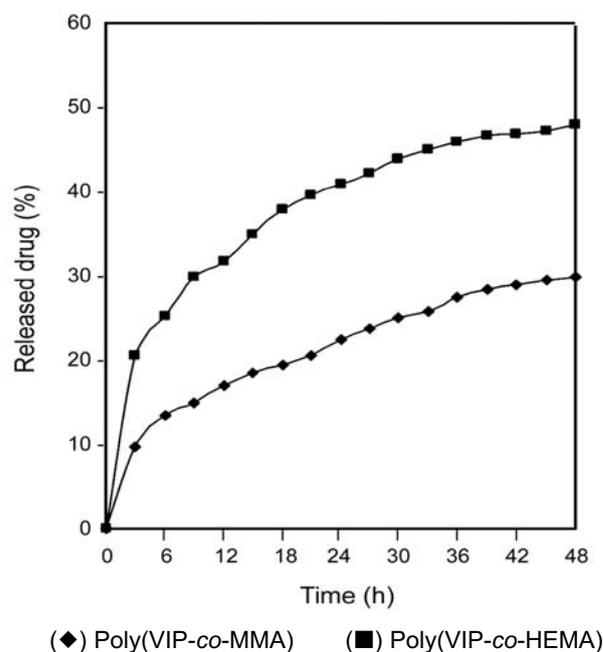
The release rate of ibuprofen from polymeric prodrugs in alkaline medium is higher than in acidic condition. It seems that polymeric prodrugs have a low degree of swelling in the acidic medium and the drug is protected against hydrolysis. The degree of hydrolysis increases as the polymer passes from acidic to alkaline medium. In alkaline pH, the polymers have reached a degree of swelling that makes the labile bonds accessible to hydrolysis. The hydrolysis mechanisms of polymeric prodrugs in various pH media are shown in Scheme III.

Different factors such as solubility of polymers and neighbouring effects of side groups can affect the overall rate of hydrolysis. The hydrophilic copolymer containing ibuprofen was hydrolyzed in buffer

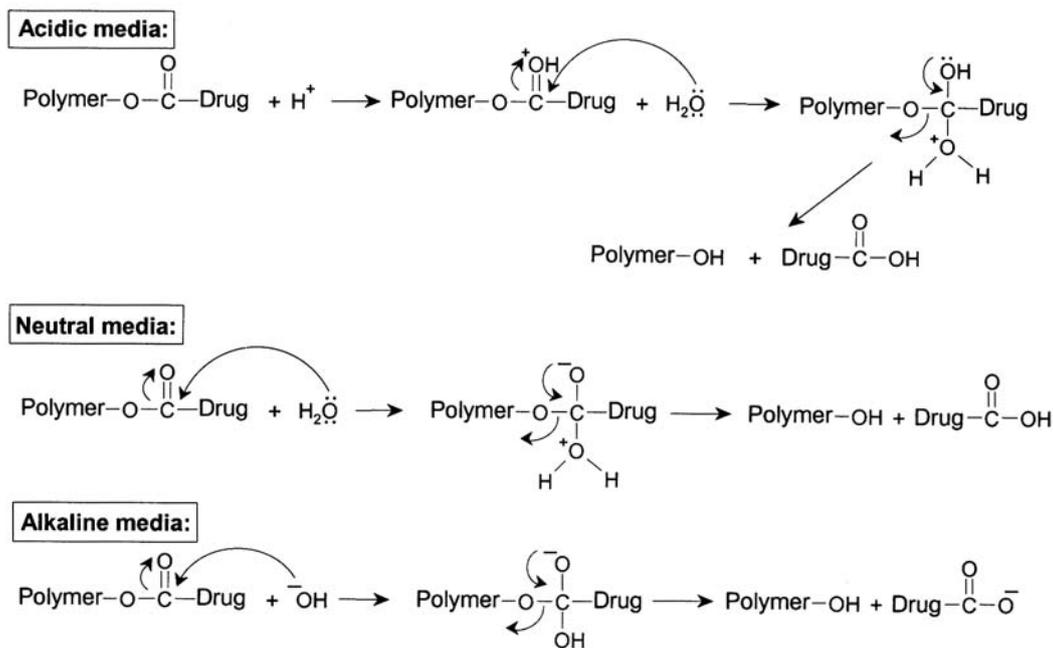


**Figure 5.** Percentage of released ibuprofen from polymeric carriers as a function of time at phosphate buffer (pH 7.4) and 37°C.

solutions rather than hydrophobic copolymer. As shown in Figures 4-6, poly(VIP-co-HEMA) is rapidly hydrolyzed because of higher hydrophilicity of



**Figure 6.** Percentage of released ibuprofen from polymeric carriers as a function of time at phosphate buffer (pH 10) and 37°C.



**Scheme III.** The hydrolysis mechanisms of polymeric prodrugs in different pH media.

HEMA units and poly(VIP-*co*-MMA) is slowly hydrolyzed because of hydrophobicity of MMA units in the copolymer structure. The results show that by passing polymeric prodrugs from acidic media to slightly alkaline pH, the labile bonds are more accessible to hydrolysis. Therefore, in alkaline pH, the polymers are easily degraded to release ibuprofen.

## CONCLUSION

In this work, VIP as a vinyl ester derivative of ibuprofen was synthesized from reaction between vinyl acetate and ibuprofen in the presence of catalyst. Then, the polymeric prodrugs containing ibuprofen pendant groups were synthesized by free radical polymerization of VIP with methacrylic monomers such as HEMA or MMA. The structure of the synthesized compounds was characterized and confirmed 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 unit along the polymer chain improves the hydrolytic behaviour. The resultant drug release profiles of the prodrugs showed that the synthesized polymeric prodrugs are pH-sensitive poly-

mers. Therefore, the studied polymers in the present investigation could 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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