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Synthesis, characterization and *in-vitro* evaluation of novel polymeric prodrugs of mefenamic acid

Mina Javanbakht[1], Mirzaagha Babazadeh[1, *]

[1]*Department of Chemistry, Tabriz Branch, Islamic Azad University, Tabriz, Iran*

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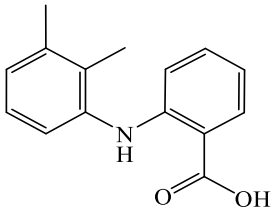
ABSTRACT

In this research work, a serious of novel polymeric prodrugs of mefenamic acid was prepared in order to minimize of the mefenamic acid side effects. Glycidyl methacrylate was first copolymerized with acrylamide and methyl methacrylate by free radical solution polymerization method, using α,ά-azobisisobutyronitrile as an initiator at 70±2 ºC. Mefenamic acid, as a non-steroidal anti-inflammatory drug, was then attached to the synthesized copolymers *via* the hydrolysable ester bonds by transesterification procedure in the presence of *N*,*N*′-dicyclohexylcarbodiimide to give polymeric prodrugs. The synthesized copolymers and polymeric prodrugs were characterized by various techniques such as FT-IR, ^{1}HNMR and ^{13}CNMR to confirm their structures. These polymeric prodrugs were hydrolyzed in cellophane membrane dialysis bags containing aqueous buffer solutions (pH 1, 7.4 and 8.5) at 37 ºC. Analysis of the hydrolyzing solutions by UV spectrophotometer at selected intervals showed that the drug could be released by selective hydrolysis of the ester bond from side chain of drug moiety. The release profiles of drug indicated that the hydrolytic behavior of polymeric prodrugs strongly depends on the hydrophilicity of polymer and the release rate of mefenamic acid at alkaline medium is higher than other mediums. These developed systems would be useful for the development of pH-sensitive polymeric prodrugs in controlled release systems.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid are widely used as therapeutic agents that have anti-inflammatory, analgesic, and antipyretic activities [1, 2]. Mefenamic acid (Scheme 1) in the form of tablet and suspension has a wide range of gastrointestinal disorders, like gastrointestinal bleeding and gastric upset. Mefenamic acid has undesirable physico-chemical properties including its poor solubility in water [3]. Various strategies for overcome the problems arising from its poor aqueous solubility and to attain improved bioavailability have been reported in literature, including reducing the particle size, solid dispersion, inclusion complex formation, solubilization in surfactant system, using prodrugs, lipid-based formulation, and self-emulsifying drug delivery systems [4].



Scheme 1. Structure of mefenamic acid .

Usually the term “prodrug” implies a product formed by a covalent bond between the drug molecule and a carrier moiety. Thus, the prodrug concept involves chemical modification of drug molecules to

∗ Corresponding author.; e-mail: babazadeh@iaut.ac.ir
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produce bio-reversible derivatives with the aim of altering physicochemical properties, optimizing drug-delivery and consequently improving drug efficacy [5-9]. The polymeric prodrug system is also referred to as the polymer drug carrier or a macromolecular-drug carrier when a reactive reagent must be released to achieve the desired activity. Prodrugs are usually prepared by polymerization of a known drug that has been slightly modified to effect the labile attachment to the polymer back-bone such a device can be made to release a drug at a controlled rate over extended periods of time by the cleavage of a chemical bond, which has several advantages. The main advantages include: (1) an increase in water solubility of low soluble or insoluble drugs, and therefore, enhancement of drug bioavailability; (2) protection of drug from deactivation and preservation of its activity during circulation, transport to targeted organ or tissue and intracellular trafficking; (3) an improvement in pharmacokinetics; (4) a reduction in antigenic activity of the drug leading to a less pronounced immunological body response; (5) the ability to provide passive or active targeting of the drug specifically to the site of its action; (6) the possibility of forming a complex advanced 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 [10-15]. Due to these advantages over to free form of a drug, the polymeric prodrug conjugates have led to a new era of polymeric drug delivery.

The main purpose of this research is design and *in-vitro* hydrolysis of new mefenamic acid polymeric prodrugs based on glycidyl methacrylate copolymers as novel controlled drug delivery systems. The influence of neighboring groups with various hydrophilic effects on drug release from polymeric carriers is investigated.

2. Materials and methods

2.1. Materials

Mefenamic acid, 2-[(2,3-dimethylphenyl)amino] benzoic acid, was kindly supplied by Zahravi pharmaceutical company (Tabriz-Iran). Glycidyl methacrylate (GMA), acrylamide (AAm), methyl methacrylate (MMA) and *N*,*N*′-dicyclohexylcarbodi-imide (DCC) were obtained from Merck and used as received. α,ά-Azobisisobutyronitrile (AIBN) was obtained from Fluka and recrystallized twice from methanol. Dimethylformamide (DMF) was purchased from Merck, 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

Fourier transform infrared (FT-IR) spectra were recorded over the range of 400-4000 cm^{-1} with a Bruker Tensor 27 series FT-IR spectrometer using KBr pellets. ^{1}HNMR and ^{13}CNMR spectra were recorded on Burker 400 MHz spectrometer in DMSO-d_6 solution. The amount of released mefenamic acid was determined by a 2100 Shimadzu UV spectrophotometer at the maximum adsorption of the free mefenamic acid (λ_{max}=285 nm) in various aqueous buffered solutions using a 1-cm quartz cell [16].

2.3. Copolymerization of GMA with acrylic-type monomers: general procedure

In two Pyrex glass polymerization ampoules, a mixture of 1.4 g (10 mmol) of GMA, 0.066 g (0.4 mmol) of AIBN as a initiator and 2.13 g (30 mmol) of AAm or 3.0 g (30 mmol) of MMA were separately dissolved in 15 ml of dried DMF. The ampoules were then degassed, sealed under vacuum, maintained at 70±2 °C in a water bath and shaken by a shaker machine for about 20 h. After this time, the obtained viscous solutions were poured into 150 ml of cooled methanol as non-solvent. The white solid precipitates of the synthesized poly(GMA-*co*-AAm) and poly(GMA-*co*-MMA) were separately collected by filtration, washed with non-solvent for several times and dried under vacuum at room temperature.

2.4. Attaching of mefenamic acid to the synthesized copolymers: esterification procedure

In a two-necked flask containing two dropping funnels, 2.4 g (10 mmol) of mefenamic acid was dissolved in 15 ml of dried DMF and cooled until 0-5 °C by ice-water bath. A solution of 2.0 g (10 mmol) of DCC dissolved in 10 ml of dried DMF was added dropwise into flask solution and stirred at 0-5 °C for 10 min. Then, 1 g of the synthesized poly(GMA-*co*-AAm) or poly(GMA-*co*-MMA) was dissolved in 10 ml of dried DMF and added dropwise with stirring to the flask mixture at the mentioned temperature. The reaction mixture was slowly returned to room temperature, stirred vigorously about 12 h and filtered for removing white precipitate of *N*,*N*-dicyclohexylurea (DCU). The remaining solution was then added dropwise into 150 ml of cooled methanol as non-solvent. The precipitated polymer-drug conjugates were collected by filtration, washed several times with methanol and dried under vacuum at room temperature.

2.5. In-vitro drug release study

The polymer-drug conjugates were dried under vacuum at room temperature and sieved with a 200 mesh sieve. Each of dried polymer-drug conjugates (20 mg) was poured into 5 ml of aqueous buffered solution (pH 1, 7.4 and 8.5) at 37 °C 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 °C. The external solution was continuously stirred and 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 at drug λ_{max} (285 nm) and determined from the calibration curve obtained previously under the same conditions. In each concentration measurement, an equal volume of fresh buffer is added into hydrolysis solution and the dilution of hydrolysis solution occurs during hydrolysis process. Therefore, for calculation of the mean concentration of released drug, each concentration measurement was corrected according to below equation:

$$C_n = C_{n.meas} + \frac{\Delta V}{V_{total}} \sum_{i=1}^{i=n-1} C_{i.meas} \quad (1)$$

where, n indicates the n^{th} concentration measurement, V_{total} is the total volume of hydrolysis solution (25 ml), ΔV is the withdrawn volume at each measurement (3 ml), $C_{n.meas}$ is the obtained drug concentration at the n^{th} measurement, and C_n is the corrected drug concentration in the hydrolysis solution due to introduction of a volume ΔV of buffer.

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 HCl (1 N) 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 was evaporated. The residue was characterized by melting point measurement and IR spectroscopy and showed that the hydrolysis product is mefenamic acid; m.p. 229 °C, IR (KBr, cm^{-1}) 3400 (N-H), 3200-2900 (O-H acid), 1660 (C=O carboxylic acid), 1580(C=C aromatic).

3. Results and discussion

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 [17].

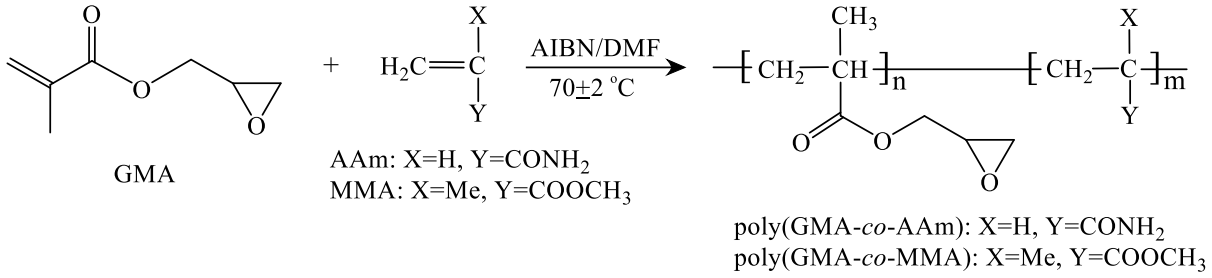
Mefenamic acid, like diclofenac has a secondary amine group in its structure, and when it is converted into a suitable polymerizable monomer, the resulting monomer does not polymerized by free radical polymerization method. Because, amine group acts as an inhibitor and prevents from radical polymerization of monomer. Therefore, for preparation of polymeric prodrugs, mefenamic acid must be bounded to performed polymers by chemically links [18].

3.1. Synthesis and characterization of GMA copolymers

GMA was respectively copolymerized with AAm and MMA in dried DMF solutions at 70±2 °C, using AIBN as a free radical initiator (Scheme 2). The preparation conditions of the synthesized copolymers are shown in Table 1.

Table 1. The preparation conditions of the synthesized copolymers

sample	$[M_1]$ (mmol/L)	$[M_2]$ (mmol/L)	non-solvent	yield (%)
poly(GMA-*co*-AAm)	GMA (10)	AAm (30)	methanol	65
poly(GMA-*co*-MMA)	GMA (10)	MMA (30)	methanol	63



Scheme 2. Copolymerization of GMA with AAm and MMA.

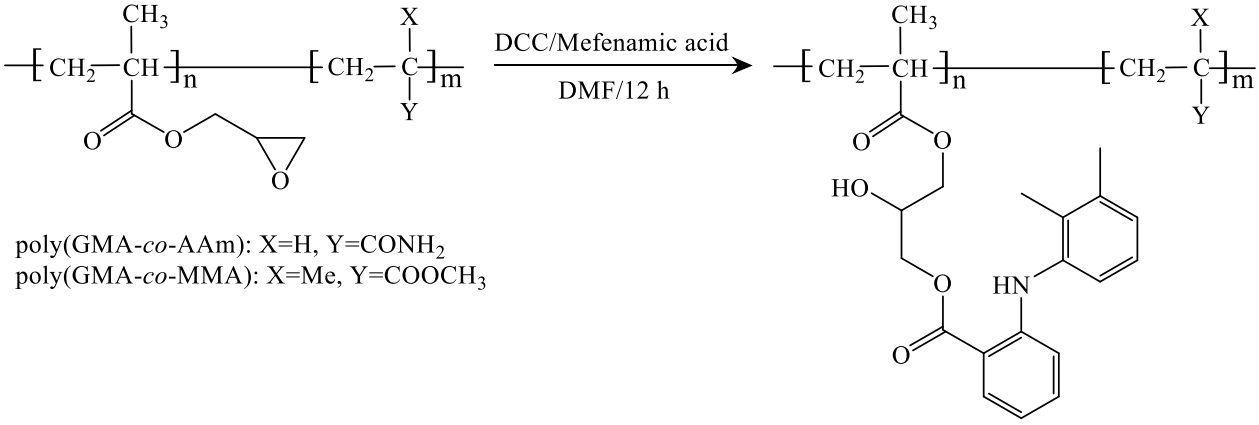
The FT-IR spectra of the synthesized copolymers showed a peak at 1735 cm^{-1} due to ester carbonyl stretching vibrations of GMA and MMA units. Also, C-O vibrations of epoxide groups in GMA units appeared at 1250 cm^{-1}. In poly(GMA-*co*-AAm), the N-H and carbonyl stretching vibrations of amide group in AAm units were respectively observed at 3300 and 1680 cm^{-1}.

In the ^{1}HNMR spectra of the copolymers, the epoxide protons are seen at 2.6, 2.8, and 3.2 ppm. Also, methylene protons of -COOC*H*$_2$- in copolymers appeared at 4.1 ppm. The proton signals of -CON*H*$_2$ in poly(GMA-*co*-AAm) and methyl protons of -COOC*H*$_3$ in poly(GMA-*co*-MMA) were seen at 9.9 and 3.8 ppm, respectively. The broad signal at 0.9-2.5 ppm was due to the methylene protons of backbone and other alkyl protons in copolymers.

In ^{13}CNMR spectra of the synthesized copolymers, the resonance signals of the ester carbonyl carbons of poly(GMA-*co*-MMA) and the amide carbonyl carbons of poly(GMA-*co*-AAm) were seen at 178.2 and 180.5 ppm, respectively. The methyne and methylene carbon atoms of the epoxy ring gave signals at 48.8 and 44.7 ppm, respectively. The methylene carbon attached to the epoxy ring appeared at 65.8 ppm. The resonance signal at 61.5 ppm was attributed to the methyl carbons of OCH_3 in MMA units. The α-methyl carbons of GMA and MMA units appeared at 16-19 ppm. The signals due to the polymer backbone carbon atoms were observed at 35-43 ppm [19-20].

3.2. Attaching of the Mefenamic acid to the synthesized copolymers

Mefenamic acid was easily attached to the synthesized copolymers by transesterification procedure in the presence of DCC as a water absorbent. The epoxide group of GMA during a ring opening reaction reacted with carboxyl group of mefenamic acid and gave a new hydroxyl group and ester bond (Scheme 3). The resulted water was absorbed by DCC and produced DCU as a white precipitate. After the completion of the reaction, the white precipitate was isolated and each solution was poured in proper non-solvent. The copolymers containing mefenamic acid were filtered, dried in vacuum at room temperature and collected in high yields (between 75-80%).



Scheme 3. Attaching of mefenamic acid to polymeric prodrugs.

In the FT-IR spectra of polymeric prodrugs, the peak due to C-O vibrations of epoxide groups in GMA units at 1250 cm^{-1} disappeared and a new peak at 3400 cm^{-1} due to O-H stretching vibration appeared. The C-H and C=C stretching vibrations of the aromatic rings were observed at 3030 and 1600 cm^{-1}, respectively. The peaks at 2990 and 2950 cm^{-1} were attributed to the asymmetrical and symmetrical C-H stretching of methylene and methyl groups. The ester carbonyl stretching was observed at 1730 cm^{-1}. The asymmetrical and symmetrical bending vibrations of methyl groups were seen at 1453 and 1380 cm^{-1}, respectively.

The ^{1}HNMR spectra of the mefenamic acid-linked copolymers showed that the ring-opening reaction results in the disappearance of epoxide proton resonances at 2.6, 2.8, and 3.2 ppm. One proton of the new formed hydroxyl group appeared at 5.0 ppm. Also, a new signal related to one amine proton of mefenamic acid appears at 9.5 ppm. The proton signals of the aryl groups in mefenamic acid were seen between 6.5 and 8.0 ppm.

In ^{13}CNMR spectra of the polymeric prodrugs, the appearance of the peak at 65.0 ppm was assigned to the carbon carrying the hydroxyl group. Also, the aromatic carbons gave signals at 110-155 ppm. The methyl carbons of mefenamic acid appeared at 19-20 ppm. The resonance of carbonyl carbon of new ester bond between polymer and drug was observed at 168 ppm.

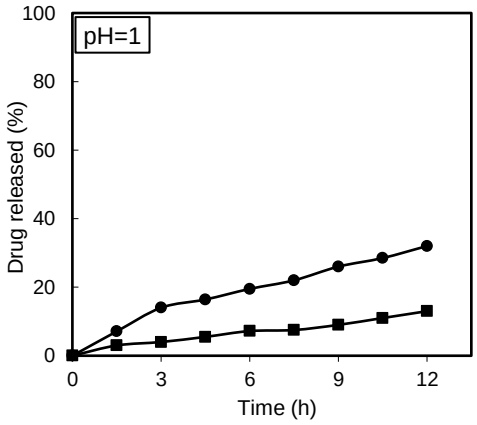
3.3. Drug release by hydrolysis of polymeric prodrugs

In order to study potential application of the mefenamic acid pendent copolymers as pharmaceutically active compounds, the in vitro hydrolysis behavior of the polymeric prodrugs was studied in aqueous phosphate buffer at 37 ºC. 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 [21-26]. The polymer-drug conjugates were dispersed in buffer solution and their hydrolysis 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 detected by an UV spectrophotometer at 285 nm. Two hydrolysable ester bonds are present in copolymers. Detection of hydrolysis solution by UV spectroscopy showed that polymer-drug conjugates release the drug gradually under various conditions by hydrolysis of the ester bond between drug and side chain of polymer during the hydrolysis time (12 h). The direct ester linkage to the main chain of polymer was less susceptible towards hydrolysis. This could be related to the steric hindrance of bulk polymer chains and decrease in bond mobility. Schemes 4-6 show the degree of hydrolysis of 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 8.5). The order of hydrolysis was as follows:

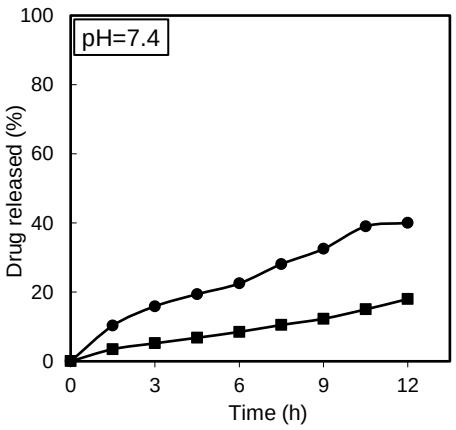
poly(GMA-*co*-AAm)-drug>poly(GMA-*co*-MMA)-drug

Different factors such as solubility of polymers and neighboring effect of side groups can affect the overall rate of hydrolysis. The hydrophilic polymer-drug was hydrolyzed in buffer solution rather than the hydrophobic systems. As shown in Scheme 4, poly(GMA-*co*-AAm)-drug was hydrolyzed rather than poly(GMA-*co*-MMA)-drug, which is related to high hydrophilicity of AAm units. The obtained results suggest that these systems could be useful for preparation of a controlled release formulation of mefenamic acid.

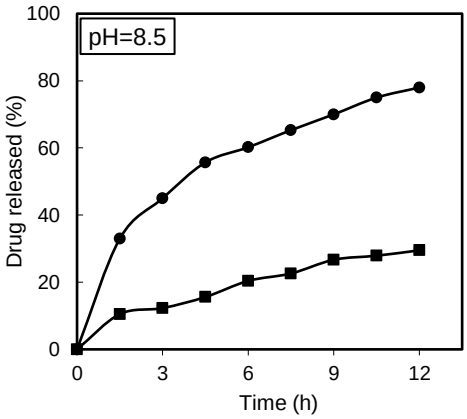
The obtained results showed that the release rate of mefenamic acid from polymeric prodrugs at alkaline medium was higher than the release rate of drug in acidic condition. The drug- release rate from polymeric prodrugs at acidic pH is very low. It seems that polymeric prodrugs have low degree of swelling in acidic medium and the drug is protected against hydrolysis. Also, at acidic media, the carboxyl group of hydrolyzed mefenamic acid will be protonated and its aqueous solubility will be lower than in alkali media, where the acid group is deprotonated.



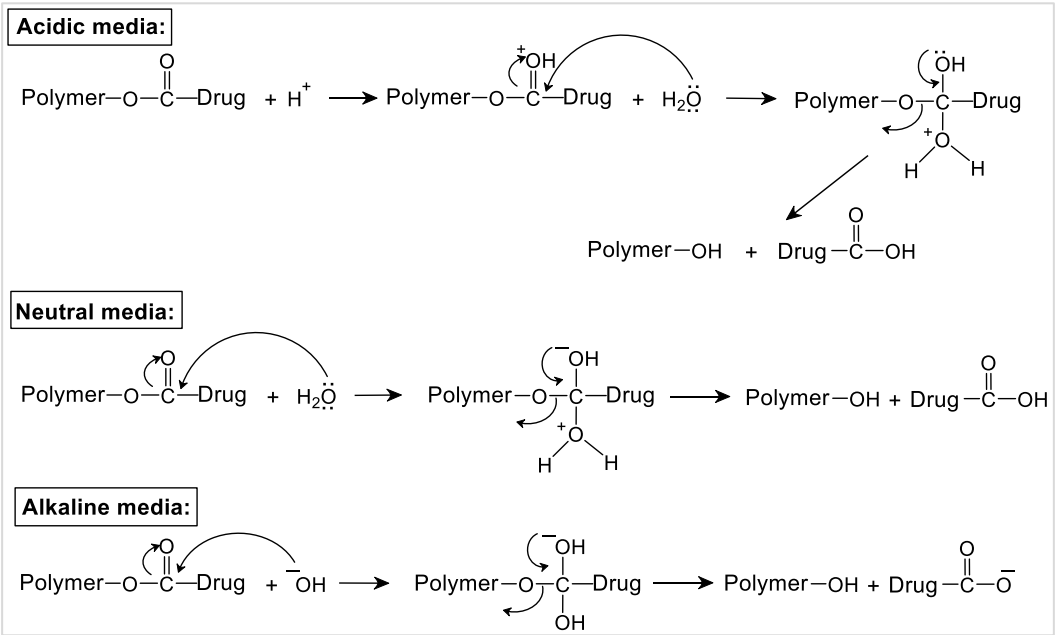
Scheme 4. Percent of drug released from polymeric carriers as a function of time at (pH 1) in 37 ºC.
● poly(GMA-*co*-AAm); ■ poly(GMA-*co*-MMA)



Scheme 5. Percent of drug released from polymeric carriers as a function of time at (pH 7.4) in 37 ºC.
● poly(GMA-*co*-AAm); ■ poly(GMA-*co*-MMA)



Scheme 6. Percent of drug released from polymeric carriers as a function of time at (pH 8.5) in 37 ºC.
● poly(GMA-*co*-AAm); ■ poly(GMA-*co*-MMA)



Scheme 7: The hydrolysis mechanism of polymeric prodrugs in different pH media.

Also, the hydrolysis of ester in acidic media is actually an equilibrium reaction, as ester formation is also catalyzed by acid (Scheme 7). 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 liable bonds accessible to hydrolysis. Therefore, in alkaline pH value, the polymers are easily degraded to release of indomethacin [27]. The hydrolysis mechanism of polymeric prodrugs in different pH conditions is shown in Scheme 7.

4. Conclusions

In this research work, we prepared new polymeric prodrugs containing mefenamic acid pendent by reacting mefenamic acid with GMA polymers. The structure of the synthesized polymers was characterized by various spectroscopy techniques. Hydrolysis studies were carried out under the similar physiological conditions in various pH (1, 7.4 and 8.5). The results showed that the ester group between the drug moiety and side chain of the polymers is hydrolyzed during the hydrolysis time. Also, the hydrolytic behavior of

polymeric prodrugs is improved by introducing hydrophilic units along the polymer chains. However, the development of such systems into a drug product will require a truly multidisciplinary approach. The developed systems would be useful for the development of pH-sensitive polymeric prodrugs for controlled release systems. The results showed that the release rate of mefenamic acid from polymeric prodrugs at alkaline medium was higher than other mediums. As the main purpose of polymeric prodrugs is the achievement of controlled drug release or slow release, the application of these polymers as drug delivery systems is expected after *in-vivo* examinations.

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