Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 356 (2008) 167–173
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Design, synthesis and in vitro evaluation of vinyl ether type polymeric prodrugs of ibuprofen, ketoprofen and naproxen

Mirzaagha Babazadeh *

Laboratory of Organic Chemistry Research, Department of Applied Chemistry, Faculty of Basic Sciences, Islamic Azad University, Tabriz Branch, P.O. Box 1655, Tabriz, Iran

Received 29 July 2007; received in revised form 5 December 2007; accepted 7 January 2008
Available online 12 January 2008

Abstract

2-(1-Propene)oxyethyl phthalimide (**3**) was synthesized from reaction of 1-(2-chloroethoxy)propene (**2**) with potassium-*t*-butoxide and polymerized by cationic polymerization method using $BF_3{\cdot}OEt_2$ as an initiator at −78 °C to obtain polymer **4**. Then, polymer **4** was hydrazinolized by hydrazine and gave polymer **5** containing pendent amine groups. Three non-steroidal anti-inflammatory drugs (NSAIDs), ibuprofen, ketoprofen and naproxen were covalently linked to polymer **5** through amide groups by reacting chloroacylated drugs **6a–6c** with amine groups of polymer **5** to obtain three polymeric prodrugs **7a–7c**. All the synthesized compounds were characterized by FT-IR, ^1H and ^{13}C NMR spectroscopy techniques. The polymer–drug conjugates were hydrolyzed in cellophane member dialysis bags containing aqueous buffered solutions (pH 1, 7.4 and 10) at 37 °C and the hydrolysis solutions were detected by UV spectrophotometer at selected intervals. The results showed that the drugs could be released by hydrolysis of the amide bonds. The release profiles indicated that the hydrolytic behavior of polymeric prodrugs strongly depends on the pH of the hydrolysis solution. The results suggested that the vinyl ether type polymers could be the useful carriers for release of profens in controlled release systems.

Keywords: Ibuprofen; Ketoprofen; Naproxen; Vinyl ether polymers; Polymeric prodrugs; Controlled release

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 (Ringsdorf, 1978; Banker, 1984; Harris, 1984; Lewis, 1990). Polymeric prodrug is a conjugation of a drug with a polymer, 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 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 led into a new era of polymeric drug delivery systems (Nichifor et al., 1997; Hoste et al., 2004; Khandare and Minko, 2006; Babazadeh et al., 2007).

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 (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.

* Tel.: +98 411 3318681; fax: +98 411 3318687.
E-mail address: babazadeh@iaut.ac.ir.

0378-5173/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2008.01.003

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).

2-Arylpropionic acids (i.e. profens), such as ibuprofen, ketoprofen and naproxen are an important class of non-steroidal anti-inflammatory drugs, which are widely used for alleviation of pain and inflammation associated with tissue injury (Caldwell et al., 1988; Cai et al., 2006). Previous pharmacological studies of profens have indicated that gastrointestinal side effects are the most frequent adverse reactions due to the acidic moiety (Tammara et al., 1993). In recent years, some NSAIDs such as ibuprofen (Davaran and Entezami, 1997a; Chang et al., 1998; Davaran and Entezami, 1998; Kim et al., 2005; Babazadeh, 2006), 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; Babazadeh, 2007) have been chemically attached to various polymer backbones and their hydrolytic behaviors studied.

This present work develops an efficient chemical method to design and synthesize new vinyl ether type polymeric carriers for release of three profens in controlled release systems. First, 3-(2-chloroethoxy)propene (**1**) was synthesized and isomerized to 1-(2-chloroethoxy)propene (**2**) in the presence of potassium-*t*-butoxide. Then, the obtained compound **2** was reacted with potassium phthalimide and gave 2-(1-propene)oxyethyl phthalimide (**3**), which polymerized by cationic polymerization method using $BF_3{\cdot}OEt_2$ at −78 °C. The obtained polymer **4** was hydrazinolized in mixture of dioxane/methanol and reacted with chloroacylated profens **6a–6c** to synthesize three polymeric prodrugs **7a–7c**. The release of profens from polymeric prodrugs was studied *in vitro* by hydrolysis in buffered solutions at different pH values and their obtained results are discussed.

2. Materials and methods

2.1. Instrumental measurements and materials

Infrared spectra were recorded by use of KBr pellets on a Shimadzu FT-IR 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 drugs was determined by a 2100 Shimadzu UV spectrophotometer at 220 nm for ibuprofen, 250 nm for ketoprofen and 232 nm for naproxen (Cai et al., 2006). Molecular weight of polymer was 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 of 2600 and 885,000. Elemental analyses were carried out with a Heareus CHN-ORAPID instrument. The cellophane membrane dialysis bag, with a molecular weight cut-off 2000 (Sigma, St. Louis), was used as provided.

Ibuprofen (2-(4-isobutylphenyl) propionic acid), ketoprofen (2-(3-benzoylphenyl) propionic acid) and naproxen (2-(6-methoxy-2-naphtyl) propionic acid) were purchased from Aldrich. *N*,*N*-Di-methylformamide (DMF) was dried over anhydrous $MgSO_4$ for 2 days and distilled under reduced pressure. All other chemicals were of reagent grade or purer.

2.2. Synthesis of 3-(2-chloroethoxy)propene (*1*)

A mixture of 2.0 g (24 mmol) of chloroethanol, 0.5 g (12.5 mmol) of NaOH, 1 g (12.5 mmol) of allyl chloride and 0.1 g (0.3 mmol) of tetrabutylammonium hydroxide (TBAH) was dissolved in 200 ml of toluene and 40 ml of DMSO. The solution was stirred at 80 °C for 20 h and then washed with an aqueous 10% NaOH solution and water. The organic phase was separated and dried with anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give 1.35 g (57%) of compound **1**. FT-IR (cm^{-1}): 3030 (=C–H), 2950, 2890 (C–H aliphatic), 1630 (C=C vinyl), 1150 (C–O). ^{1}H NMR ($CDCl_3$ with tetramethylsilane, ppm): 3.6 (t, 2H, –O–CH_2–C–Cl), 3.9 (t, 2H, –CH_2Cl), 4.1 (d, 2H, =C–CH_2–O–), 5.0 (d, 1H, CH_2=C–), 5.2 (d, 1H, CH_2=C–), 5.7 (m, 1H, C=CH–). ^{13}C NMR ($CDCl_3$ with tetramethylsilane, ppm): 42.7 (1C, –$\underline{C}H_2$Cl), 71.4 (1C, –O–$\underline{C}H_2$–CH_2–) 71.8 (1C, =CH–$\underline{C}H_2$–O–), 116.2 (1C, $\underline{C}H_2$=CH–), 133.2 (1C, CH_2=$\underline{C}$H–). Elemental analysis for C_5H_9ClO (120.5) (%): calcd. C 49.8, H 7.5; found: C 50.1, H 7.3.

2.3. Synthesis of 1-(2-chloroethoxy)propene (*2*)

A mixture of 6.0 g (50 mmol) of compound **1**, 25 mmol of potassium-*t*-butoxide and 50 ml 0f DMSO was stirred at 75 °C under dry argon for 15 min. Then the solution was diluted with 50 ml of water and the organic phase extracted with 150 ml of CH_2Cl_2. The residue was dried with anhydrous $MgSO_4$ and the solvent removed under reduced pressure to give 6 g (98%) of compound **2**. FT-IR (cm^{-1}): 3030 (=C–H), 2950, 2890 (C–H aliphatic), 1630 (C=C vinyl), 1150 (C–O). ^{1}H NMR ($CDCl_3$ with tetramethylsilane, ppm): 1.7 (d, 3H, –CH_3), 3.7 (q, 1H, Me–CH=), 3.9 (t, 2H, –OCH_2–), 4.7 (t, 2H, –CH_2Cl), 5.9 (d, 1H, =CH–O–). ^{13}C NMR ($CDCl_3$ with tetramethylsilane, ppm): 11.2 (1C, –$\underline{C}H_3$), 42.5 (1C, –$\underline{C}H_2$Cl), 72.3 (1C, –O$\underline{C}H_2$–), 101.5 (1C, CH_3–$\underline{C}$H=), 146.5 (1C, =$\underline{C}$H–O–). Elemental analysis for C_5H_9ClO (120.5) (%): calcd. C 49.8, H 7.5; found: C 48.6, H 7.8.

2.4. Synthesis of 2-(1-propene)oxyethyl phthalimide (*3*)

A mixture of 5.9 g (49 mmol) of compound **2**, 48 g (27 mmol) of potassium phthalimide, 1 g (3 mmol) of tetrabutylammonium bromide (TBAB) as a phase transfer catalyst was dissolved in 150 ml of DMF and stirred in 100 °C for 6 h. After this time, the mixture was cooled to the room temperature and the precipitated potassium chloride filtered off. The solution was poured into 500 ml of water and the precipitated yellowish solid collected. The obtained powder was recrystallized from methanol to give 5.5 g (48%) of compound **3**. FT-IR (KBr, cm^{-1}): 3050 (C–H aromatic), 3030 (C–H vinylic), 2950, 2890 (C–H aliphatic), 1680 (C=O amide), 1630 (C=C vinyl), 1600, 1480 (C=C aromatic), 1150 (C–O). ^{1}H NMR ($CDCl_3$ with tetramethylsilane, ppm): 1.7 (d, 3H, –CH_3), 3.9 (t, 2H, –CH_2O–), 4.2 (q, 1H,

Me–CH=), 4.4 (t, 2H, –CH_2N–), 5.7 (d, 1H, –C=CH–O–), 7.8–8.1 (m, 4H, Aryl-H). ^{13}C NMR ($CDCl_3$ with tetramethylsilane, ppm): 11.0 (1C, –$\underline{C}H_3$), 36.2 (1C, –$\underline{C}H_2$N), 66.8 (1C, –O$\underline{C}H_2$), 104.2 (1C, CH_3–$\underline{C}$H=), 123.1, 130.4, 134.3 (6C, Aryl), 147.1 (1C, =$\underline{C}$H–O–), 167.5 (2C, –C=O). Elemental analysis for $C_{13}H_{13}NO_3$ (231) (%): calcd. C 67.5, H 5.6, N 6.0; found: C 67.1, H 5.2, N 6.3.

2.5. Polymerization of **3** to obtain polymer **4**

A mixture of 3.25 g (10 mmol) of compound **3** and 10 mmol of $BF_3{\cdot}OEt_2$ as an initiator was dissolved in 50 ml of CH_2Cl_2 and stirred at −78 °C under dry argon. After 1 h, the reaction was terminated by adding ammoniacal methanol and a solution of 10% sodium thiosulfate added. The organic phase was separated and dried with anhydrous $MgSO_4$. The dried solution was gradually added into 100 ml of cooled methanol and the precipitated polymer collected. The precipitate was washed with the same precipitant and dried under vacuum at room temperature to give 2.1 g (64%) of polymer **4**. FT-IR (KBr, cm^{-1}): 3050 (C–H aromatic), 2950, 2890 (C–H aliphatic), 1680 (C=O amide), 1600, 1480 (C=C aromatic), 1150 (C–O). ^{1}H NMR (DMSO-d_6 with tetramethylsilane, ppm): 1.1 (3H, –CH_3), 2.0 (1H, Me–CH–), 3.1 (1H, –CH–O–), 3.7 (2H, –CH_2O–), 3.9 (2H, –CH_2N–), 7.6–8.1 (4H, Aryl-H). ^{13}C NMR (DMSO-d_6 with tetramethylsilane, ppm): 11.5 (1C, –$\underline{C}H_3$), 29.5 (1C, Me–$\underline{C}$H–), 36.8 (1C, –$\underline{C}H_2$N–), 66.5 (1C, –O$\underline{C}H_2$–), 69.3 (1C, –$\underline{C}$H–O–), 122.8, 131.2, 134.9 (6C, Aryl), 166.9 (2C, C=O).

2.6. Hydrazinolysis of polymer **4** to obtain polymer **5**

To a mixture of 0.5 g of polymer **4** in 20 ml of dioxane and 10 ml of methanol, 1 ml of hydrazine monohydrate was added and refluxed for 3 h. The obtained white precipitate (the polymeric ammonium salt of phthalylhydrazide) was isolated by evaporation of the solvent in rotary evaporator. Then, HCl (0.5 N) was added to the resulted salt and refluxed for 15 min. The solution was diluted with 10 ml of water and heated for 45 min. The resulted heterogeneous mixture was concentrated to about 3 ml by evaporation and the insoluble byproduct was removed by filtration. The filtrate was neutralized with NaOH (2 N) and evaporated. The residue was dissolved in 5 ml of methanol and filtrated to remove NaCl. Then, methanol was evaporated by rotary evaporator to give polymer **5** (85% yield). FT-IR (KBr, cm^{-1}): 3320, 3250 (N–H amine), 2950, 2890 (C–H aliphatic), 1150 (C–O). ^{1}H NMR (DMSO-d_6 with tetramethylsilane, ppm): 1.0 (3H, –CH_3), 2.0 (1H, Me–CH–), 2.3 (2H, –NH_2), 2.7 (2H, –CH_2N), 3.2 (1H, –CH–O–), 3.6 (2H, –CH_2O–). ^{13}C NMR (DMSO-d_6 with tetramethylsilane, ppm): 11.0 (1C, –$\underline{C}H_3$), 29.2 (Me-$\underline{C}$H–), 42.1 (1C, –$\underline{C}H_2NH_2$), 66.8 (1C, –O–$\underline{C}H_2$), 69.5 (1C, –$\underline{C}$H–O–).

2.7. Attaching of profens to polymer **5** and synthesis of polymeric prodrugs **7a–7c**

A mixture of 40 mmol of profen such as ibuprofen (**a**), ketoprofen (**b**) or naproxen (**c**) and 25 ml of thionyl chloride was refluxed in a steam bath for 2 h. The excess thionyl chloride was azeotropically removed with dry benzene under reduced pressure to obtain the related chloroacylated profens **6a–6c** (Davaran and Entezami, 1998). Then, 50 mmol of each chloroacylated profens was separately dissolved in 30 ml of dry DMF and added to a solution of 2.5 g of polymer **5** dissolved in 70 ml of DMF and 10 ml of pyridine. The mixture was stirred for 40 h at room temperature and poured into 100 ml of cooled methanol. The precipitated polymers **7a–7c** were filtered, collected and dried under vacuum, respectively. The products were characterized by FT-IR, ^{1}H NMR and ^{13}C NMR.

7a: yield 82%, FT-IR (KBr, cm^{-1}): 3300 (N–H amide), 3030 (C–H aromatic), 2950, 2850 (C–H aliphatic), 1680 (C=O amide), 1600 (C=C aromatic), 1150 (C–O). ^{1}H NMR (DMSO-d_6 with tetramethylsilane, ppm): 0.9 (6H, –$C(CH_3)_2$), 1.1 (3H, CH_3–C–C–), 1.5 (3H, CH_3–C–C=O), 1.8 (1H, –CH–Me_2), 2.2 (1H, –CH–C–O–), 2.4 (2H, –CH_2–Ar), 3.1 (1H, –CH–O), 3.4 (2H, –CH_2O–), 3.6 (2H, –CH_2N–), 3.9 (1H, –CH–Ar), 7.2-7.8 (4H, Ar-H), 9.8 (1H, –NH–C=O). ^{13}C NMR (DMSO-d_6 with tetramethylsilane, ppm): 11 (1C, $\underline{C}H_3$–CH–CH–), 19 (1C, $\underline{C}H_3$–C–Ar), 22 (2C, –C($\underline{C}H_3$)$_2$), 23 (1C, –$\underline{C}$H–Me_2), 29.5 (1C, Me–$\underline{C}$H–C–), 36 (1C, –$\underline{C}H_2$NH–), 45 (1C, Ar–$\underline{C}H_2$–), 49 (1C, Ar–$\underline{C}$H–), 64 (1C, –O$\underline{C}H_2$–), 66.6 (1C, Me–C–$\underline{C}$H–O–), 126–154 (6C, Aryl), 168 (1C, C=O amide).

7b: yield 80%, FT-IR (KBr, cm^{-1}): 3320 (N–H amide), 3030 (C–H aromatic), 2950, 2860 (C–H aliphatic), 1725 (C=O cetone), 1680 (C=O amide), 1600 (C=C aromatic), 1155 (C–O). ^{1}H NMR (DMSO-d_6 with tetramethylsilane, ppm): 1.1 (3H, CH_3–C–C–), 1.5 (3H, CH_3–C–C=O), 2.2 (1H, –CH–C–O–), 3.1 (1H, –CH–O), 3.4 (2H, –CH_2O–), 3.6 (2H, –CH_2N–), 3.9 (1H, –CH–Ar), 7.5–7.9 (9H, Ar–H), 9.8 (1H, –NH–C=O). ^{13}C NMR (DMSO-d_6 with tetramethylsilane, ppm): 11 (1C, $\underline{C}H_3$–CH–CH–), 19 (1C, $\underline{C}H_3$–C–Ar), 29.5 (1C, Me–$\underline{C}$H–C–), 36 (1C, –$\underline{C}H_2$NH–), 50 (1C, Ar–$\underline{C}$H–), 64 (1C, –O$\underline{C}H_2$–), 66.5 (1C, Me–C–$\underline{C}$H–O–), 123–141 (12C, Aryl), 168 (1C, C=O amide), 190 (1C, Aryl–$\underline{C}$O–Aryl).

7c: yield 72%, FT-IR (KBr, cm^{-1}): 3300 (N–H amide), 3030 (C–H aromatic), 2950, 2850 (C–H aliphatic), 1680 (C=O amide), 1600 (C=C aromatic), 1150 (C–O). ^{1}H NMR (DMSO-d_6 with tetramethylsilane, ppm): 1.1 (3H, CH_3–C–C–), 1.5 (3H, CH_3–C–C=O), 2.2 (1H, –CH–C–O–), 3.1 (1H, –CH–O), 3.4 (2H, –CH_2O–), 3.6 (2H, –CH_2N–), 3.9 (4H, –CH–Ar and CH_3O–), 7.4–8.2 (6H, Ar–H), 9.8 (1H, –NH–C=O). ^{13}C NMR (DMSO-d_6 with tetramethylsilane, ppm): 11 (1C, $\underline{C}H_3$–CH–CH–), 19 (1C, $\underline{C}H_3$–C–Ar), 29.5 (1C, Me–$\underline{C}$H–C–), 36 (1C, –$\underline{C}H_2$NH–), 50 (1C, Ar–$\underline{C}$H–), 61 (1C, –O$\underline{C}H_3$), 64 (1C, –O$\underline{C}H_2$–), 66.5 (1C, Me–C–$\underline{C}$H–O–), 113–150 (12C, Aryl), 168 (1C, C=O amide).

2.8. In vitro hydrolysis method of profen prodrugs

Two hundred milligram of each dried prodrugs **7a–7c** was, respectively, poured into 5 ml of aqueous buffered solution (pH 1, 7.4 and 10) 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.

2.9. Characterization of hydrolysis products

Twenty milligram of each prodrugs **7a–7c** was, respectively, 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. The obtained results showed that the hydrolysis products were ibuprofen, ketoprofen and naproxen.

3. Results and discussion

3.1. Synthesis of vinyl ether type polymers

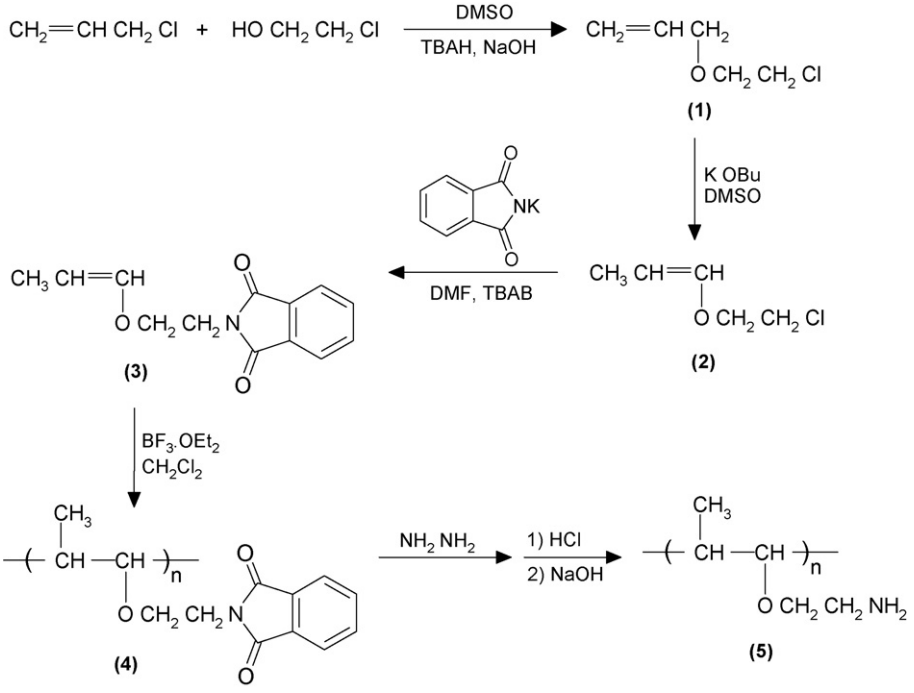
3-(2-Chloroethoxy)propene (**1**) was synthesized from reaction between allyl chloride and chloroethanol. Compound **1** was isomerized to 1-(2-chloroethoxy)propene (**2**) in the presence of potassium-*t*-butoxide. The reaction of compound **2** with potassium phthalimide gave 2-(1-propene)oxyethyl phthalimide (**3**) in a nucleophilic substitution reaction. Monomer **3** was polymerized by cationic polymerization method using $BF_3{\cdot}OEt_2$ as an initiator at −78 °C in CH_2Cl_2. Gel permeation chromatography (GPC) was used for determination of average molecular weights of the synthesized polymer **4**. The resultants showed that the number-average molecular weight and polydispersity indices of the polymer were 22,000 and 1.9, respectively. Polymer **4** was hydrazinolized by hydrazine monohydrate in the mixture of dioxane/methanol to give polymer **5** containing pendent amine groups (Scheme 1). The chemical structure of all the synthesized compounds were characterized and confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis.

3.2. Attaching of profens to polymer *5* (synthesis of polymeric prodrugs)

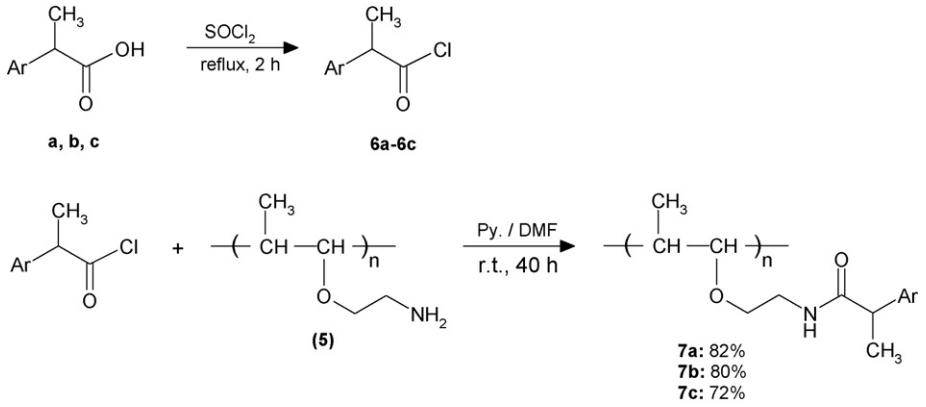
Profens (ibuprofen, ketoprofen and naproxen) were converted to the chloroacylated derivatives **6a–6c** in the presence of thionyl chloride. The obtained chloroacylated drugs were reacted with polymer **5** in a mixture of pyridine and DMF to obtain polymeric prodrugs **7a–7c**. Scheme 2 shows the synthetic route of polymeric prodrugs in which three NSAIDs have been linked to polymer through amide groups. The amine groups from polymer **5** reacted with active acyl chloride groups from chloroacylated profens to give new amide bond between drug and polymer. In these reactions, obtained HCl was absorbed by pyridine and produced pyridinium salt as a white precipitate. After completing of reactions, the white precipitate was isolated and each solution was poured in methanol as a non-solvent. The polymers containing drugs were dried and collected in high yields (between 70 and 85%).

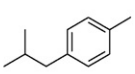
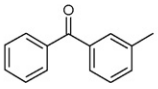
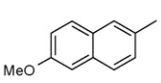
3.3. Characterization of polymeric prodrugs

Characterization data for the prepared prodrugs were obtained through a variety of techniques including FT-IR and



Scheme 1.



Drug	a	b	c
Name	Ibuprofen	Ketoprofen	Naproxen
Ar			

Scheme 2.

NMR spectroscopy. The ^{1}H NMR spectra of the drug-linked polymers showed that all the amine groups in polymer **5** have been converted to amide groups. These spectra showed that with formation of new amide bond, the peak at 2.3 ppm corresponding to two protons of amine group disappears and a new signal related to one amide proton appears at 9.8 ppm. The proton signals of the profens aryl groups were seen between 7.0 and 8.3 ppm.

In the FT-IR spectra of polymeric prodrugs, the peaks due to NH_2 stretching vibration of polymer **5** at 3320 and 3250 cm^{-1} disappeared and two new peaks at 3300 and 1680 cm^{-1} due to N–H and C=O stretching vibration of the amide group appeared, respectively. The C–H and C=C stretching vibrations of the aromatic rings were observed at 3030 and 1600 cm^{-1}, respectively.

In the ^{13}C NMR spectra of the drug-linked polymers, the resonance of carbonyl carbon of new amide bond between polymer and drug observed at 168 ppm. Also, the aromatic carbons gave signals at 110–155 ppm. A typical ^{13}C NMR spectrum of **7a** is shown in Fig. 1.

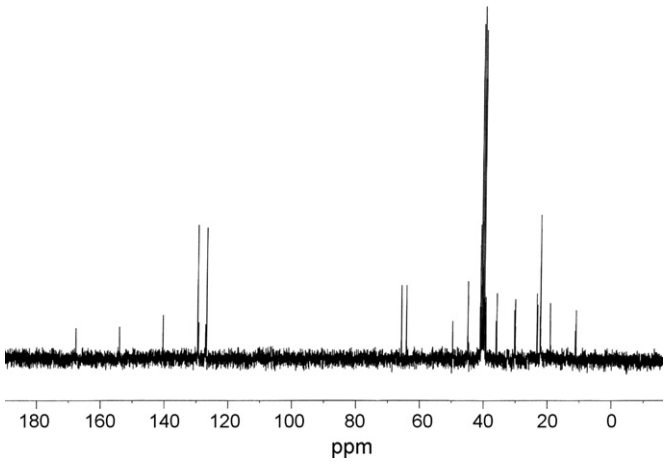


Fig. 1. ^{13}C NMR spectrum of polymeric prodrug **7a** in DMSO-d_6.

3.4. Drug release by hydrolysis of polymeric prodrugs

The *in vitro* hydrolysis behavior of drug–polymer adducts was studied in physiological conditions (aqueous phosphate or hydrochloric acid buffers, at 37 °C). Hydrolyses were 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

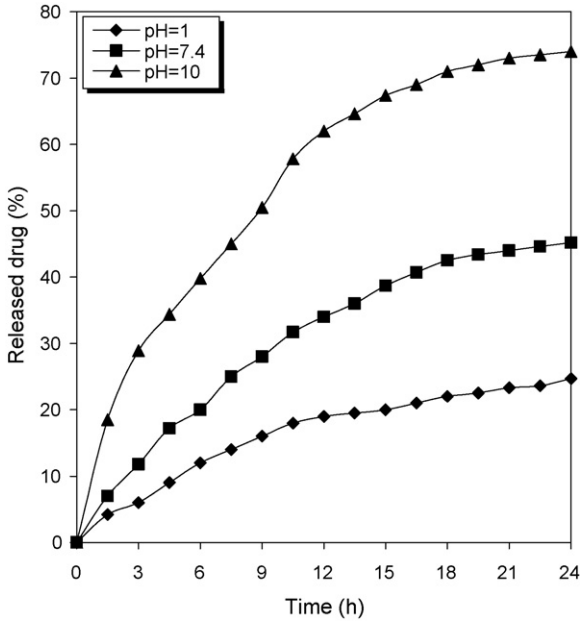


Fig. 2. Percent of released ibuprofen from polymeric prodrug **7a** as a function of time at different pH values.

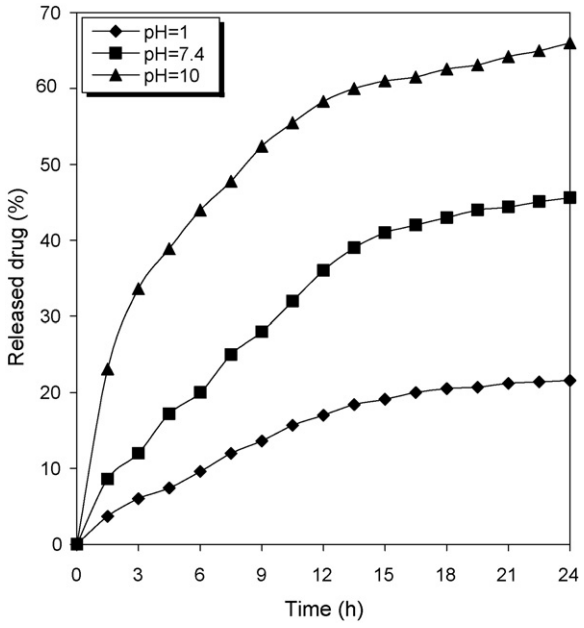


Fig. 3. Percent of released ketoprofen from polymeric prodrug **7b** as a function of time at different pH values.

determined by a UV spectrophotometer at related wavelength. Detection of the hydrolyzing solution by UV spectrophotometer showed that the amide bond between drug moiety and polymer is hydrolyzed during the reaction time (24 h). The IR spectroscopic data and melting point measurements of the residue corresponded to the free drug.

Figs. 2, 3 and 4 show the degree of hydrolysis of the polymers containing profens as function of time in HCl buffer (pH 1) and KH_2PO_4–Na_2HPO_4 buffer (pH 7.4 and 10). As shown in Figs. 2–4, the release rate of drugs from polymeric prodrugs at alkaline medium was higher than the release rate of drugs

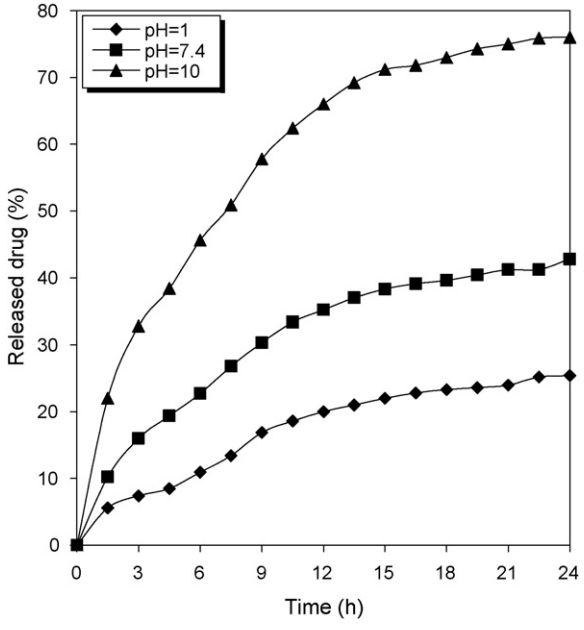


Fig. 4. Percent of released naproxen from polymeric prodrug **7c** as a function of time at different pH values.

in acidic condition. It seems that polymeric prodrugs have a low degree of swelling in the acidic medium and the drugs are 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 (Babazadeh, 2006, 2007; Babazadeh et al., 2007). Finally, the release profiles indicate that the hydrolytic behavior of polymeric prodrugs strongly depends on the pH of the hydrolysis solution.

4. Conclusion

In this work, polymeric prodrugs containing three 2-arylpropionic acid derivatives such as ibuprofen, ketoprofen and naproxen were prepared by the reaction of chloroacylated drugs with vinyl ether type polymer. The structure of polymers was characterized by various spectroscopy techniques. Study of hydrolyses was carried out similar to the physiological conditions. The results showed that the amide groups between drugs and polymer in synthesized polymeric prodrugs were hydrolyzed and the release rate of drugs 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, application of these vinyl ether type polymers as a drug delivery system is expected after *in vivo* examinations.

References

Babazadeh, M., 2006. Synthesis and study of controlled release of ibuprofen from the new acrylic type polymers. Int. J. Pharm. 316, 68–73.

Babazadeh, M., 2007. Synthesis, characterization, and in vitro drug-release properties of 2-hydroxyethyl methacrylate copolymers. J. Appl. Polym. Sci. 104, 2403–2409.

Babazadeh, M., Edjlali, L., Rashidian, L., 2007. Application of 2-hydroxyethyl methacrylate polymers in controlled release of 5-amino salicylic acid as a colon-specific drug. J. Polym. Res. 14, 207–213.

Banker, G.S., 1984. Pharmaceutical application of controlled release. In: Langer, R.S., Wise, D.L. (Eds.), Medical Application of Controlled Release, 2. CRC Press, Boca Raton, Florida, pp. 1–34.

Bonina, F.P., Motenegro, L., Capraiis, P.D., Palagiano, F., Trapani, G., Liso, G., 1995. In vitro and in vivo evaluation of polyoxyethylene indomethacin esters as dermal prodrugs. J. Control. Release 34, 223–232.

Bonina, F.P., Puglia, C., Barbuzzi, T., Caprariis, P.D., Palagiano, F., Rimoli, M.G., Saija, A., 2001. In vitro and in vivo evaluation of polyoxyethylene esters as dermal prodrugs of ketoprofen, naproxen and diclofenac. Eur. J. Pharm. Sci. 14, 123–134.

Caldwell, J., Hutt, A.J., Fournel-Gigleux, S., 1988. The metabolic chiral inversion and dispositional enantioselectivity of the 2-arylpropionic acids and their biological consequences. Biochem. Pharmacol. 37, 105–114.

Cai, X., Wang, N., Lin, X., 2006. Chemo-enzymatic synthesis of optically active polymeric prodrug of naproxen, ketoprofen and ibuprofen. Polymer 47, 6491–6495.

Chang, C.H., Sheu, Y.M., Hu, W.P., Wang, L.F., Chen, J.S., 1998. Synthesis and properties of copolymers from 2-hydroxyethyl methacrylate-linked nonsteroidal anti-inflammatory agents with methacrylic acid. J. Polym. Sci. Polym. Chem. 36, 1481–1489.

Davaran, S., Entezami, A.A., 1997a. Synthesis and hydrolysis of polyurethanes containing ibuprofen pendent groups. J. Bioact. Compact. Polym. 12, 47–58.

Davaran, S., Entezami, A.A., 1997b. Acrylic type polymers containing ibuprofen and indomethacine with difunctional spacer group: synthesis and hydrolysis. J. Control. Release 47, 41–49.

Davaran, S., Entezami, A.A., 1998. Hydrophilic copolymers prepared from acrylic type derivatives of ibuprofen containing hydrolysable thioester bond. Eur. Polym. J. 34, 187–192.

Giammona, G., Puglisi, G., Carlisi, B., Pignatello, R., Spadaro, A., Caruso, A., 1989. Polymeric prodrugs: α,β-poly(*N*-hydroxyethyl)-DL-aspartamide as a macromolecular carrier for some non-steroidal anti-inflammatory agents. Int. J. Pharm. 57, 55–62.

Harris, F.W., 1984. Controlled release from polymers containing pendent bioactive substituents. In: Langer, R.S., Wise, D.L. (Eds.), Medical Application of Controlled Release, 1. CRC Press, Boca Raton, Florida, pp. 103–128.

Hoste, K., Winne, K., Schacht, E., 2004. Polymeric prodrugs. Int. J. Pharm. 277, 119–131.

Khandare, J., Minko, T., 2006. Polymer–drug conjugates: progress in polymeric prodrugs. Prog. Polym. Sci. 31, 359–397.

Kim, H.W., Chung, C.W., Hwang, S.J., Rhee, Y.H., 2005. Drug release from and hydrolytic degradation of a poly(ethylene glycol) grafted poly(3-hydroxyoctanoate). Int. J. Biol. Macromol. 36, 84–89.

Kim, S.Y., Shin, I.G., Lee, Y.M., Cho, C.S., Sung, Y.K., 1998. Methoxy poly(ethylene glycol) and caprolactone amphiphilic block copolymeric micelle containing indomethacin: II. Micelle formation and drug release behaviours. J. Control. Release 51, 13–22.

Lewis, D.H., 1990. Controlled release of bioactive agents from lactide/glycolide polymers. In: Chasin, M., Langer, R. (Eds.), Biodegradable Polymers as Drug Delivery Systems. Marcel Dekker, New York, pp. 1–2.

Nasir Tabrizi, M.H., Davaran, S., Entezami, A.A., 1996. Synthesis of diclofenac polymeric prodrugs and their hydrolysis reactivity. Iran. Polym. J. 5, 243–249.

Nichifor, M., Schacht, E.H., Seymour, L.W., 1997. Polymeric prodrugs of 5-fluorouracil. J. Control. Release 48, 165–178.

Ringsdorf, H., 1978. Synthetic polymeric drugs. In: Kostelnic, R.J. (Ed.), Polymeric Delivery Systems. Gordon and Breach, New York, p. 197.

Tammara, V.K., Narurkar, M.M., Crider, A.M., Khan, A.M., 1993. Synthesis and evaluation of morpholinoalkyl ester prodrugs of indomethacin and naproxen. Pharm. Res. 10, 1191–1199.