Synthesis and Characterization of New Silyl Cross-Linking Agent for Drug Delivery System

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ABSTRACT: New crosslinking reagent that has silyl group together with ethyl hydroxyl methacrylate was successfully synthesized. Network polymers with this crosslinked reagent, methacrylic acid, and silyl monomers of 2-hydroxyethyl methacrylate ester were synthesized and studied their properties. These sily monomers are: 2-[(triethylsilyl)oxy] ethyl methacrylate, 2-((*tert*-butyldimethylsilyl)oxy)ethyl methacrylate, and 2-((triphenylsilyl)oxy)ethyl methacrylate. All monomers and polymers were identified by spectroscopic methods. Then mesalasine was entrapped in these network polymers and the *in vitro* release profiles were established separately in both enzyme-free simulated gastric and intestinal fluids (SGF, pH 1) and (SIF, pH 7.4), respectively. *In vitro* release studies showed that these network polymers can be good candidates for colon-specific drug delivery. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 122: 2368–2373, 2011

Key words: crosslinking; copolymers; hydrogels; drug delivery systems

INTRODUCTION

Hydrogels, which are water swollen polymer and copolymer networks, have been used in bioengineering, biotechnology, medicine, pharmacy, agriculture, food industry, photographic technology, and other fields.[1]

Hydrogels are water-swollen polymeric networks containing chemical or physical crosslinks. Physical crosslinks may be entanglements, crystallites, or weak associations such as hydrogen bonds or vander Waals interactions.[2] Hydrogels are either neutral or ionic, depending on the ionization of their pendant groups. The network morphology may be amorphous or semicrystalline. Additional network structures include hydrogen-bonded or supermolecular structures. In addition, the network structure may be cast in the form of macroporous, microporous, or nanoporous gels. In addition to their promising biocompatibility characteristics, certain hydrogels are particularly desirable in the biomedical field due to their sensitivity in the physiological or biological environment where they are used. In recent years, much research has focused on the development and analysis of environmentally responsive hydrogels, that is, hydrogels that can exhibit swelling changes due to the external pH, temperature, ionic strength, nature of the swelling agent, or electromagnetic radiation.[3]

2-Hydroxyethyl methacrylate (HEMA) based hydrogels can be polymerized easily, and they are biocompatible. PHEMA gels are very resistant to high temperatures, to acid and alkaline hydrolysis, and they have a low reactivity with amines. Such chemical and thermal stability make pHEMA gels suitable materials for the development of controlled drug delivery systems and for other biomedical and pharmaceutical applications.[4]

Attaching the organosilyl groups to macromolecular chains as a HEMA polymer should lead to important modifications of polymer properties. The combination of versatility and tailored molecules has relatively made acrylic and methacrylic esters prime candidates for diverse applications. Polymers containing organosilyl groups are an interesting research field in polymer and silicon chemistry. Attaching the organosilyl groups to macromolecular chains should lead to important modifications of polymer properties such as gas permeability and perm selectivity parameters, mechanical, thermal, and surface properties, as well as photochemical reactivity.[5–12] However, some silyl derivatives of polymers such as acrylates and styrene showed membrane properties.[13] One of the important properties of these membranes is selectivity with respect to oxygen. The membrane usually showed high oxygen permeability and a reasonably high permselectivity of oxygen against nitrogen and carbon dioxide. Thus, this type of polymers may be applicable to the biosensor electrode membrane as their chemical and

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TABLE I
The Molar Compositions and T_g Data of Cross-Linked Copolymers

Network polymers	Monomer A	Monomer B	Ratio of Monomers	Percent of DMVS	T_g(C°)
P_1	TESiEMA	HEMA	1 : 1	5%	124.5
P_2	TESiEMA	HEMA	1 : 1	10%	155
P_3	TESiEMA	HEMA	2 : 1	10%	127.5
P_4	TPhSiEMA	HEMA	1 : 1	5%	118
P_5	TPhSiEMA	HEMA	1 : 1	10%	126
P_6	TPhSiEMA	MAA	1 : 1	5%	136
P_7	TPhSiEMA	MAA	1 : 1	10%	149

physical properties are appropriate. Siloxy methacrylate was also used in contact lenses. Soft contact lenses have been proposed as a new vehicle for ophthalmic drug delivery.[14–23] theoretical simulation predicted that delivery of ophthalmic drugs by contact lenses is about 35 times more efficient than by eye drops. Other benefits include convenience for use, no blinding of the eye, eliminating side-effects, better rate of release over time, and others.[24]

The demand for novel drug delivery technologies is ever increasing. These drug delivery technologies can be broadly classified into four principle routes like oral, transdermal, inhalation, and parenteral.[25] Our essential idea is to synthesize pH-sensitive hydrogels by bulk free-radical copolymerization and to evaluate them as a drug delivery system. In this way, we prepared new silyl crosslinking reagent containing HEMA, and some network polymers. Then mesalasine (MZ) was entrapped in these network polymers. Drug release profiles from these polymers were done. *in vitro* release profiles were established separately in both enzyme-free simulated gastric and intestinal fluids (SGF, pH 1) and (SIF, pH 7.4), respectively.

EXPERIMENTAL

Synthesis of monomers and copolymers were carried out under argon to exclude oxygen and moisture from the reaction system.

Materials

The solvents and reagents were purchased from Merck and Fluka (Germany). Tetrahydrofuran (THF) was dried by a standard method and MZ, $^{t}BuMe_2SiCl$, Et_3SiCl, Me_3SiCl, Ph_3SiCl, and $Me_2(CH_2{=}CH)SiCl$ used as received.

HEMA, and methacrylic acid were distilled under reduced pressure. Initiator 2,2′-azobisisobutyronitrile (AIBN), was purified by recrystallization from methanol.

Measurements

^{1}H-NMR spectra were recorded on a Bruker 400 AC spectrometer in $CDCl_3$. The IR spectra were recorded on a Shimadzu FT-IR-408 spectrophotometer. The DSC curves were obtained on a TGA/SDTA 851 calorimeter at heating and cooling rates of 10°C/min in air.

Synthesis of crosslinking agent: 2-((dimethyl (vinyl)silyl)oxy)ethyl methacrylate (DMVS)

A mixture of 3 g (0.02 mol) HEMA and 3.5 g (0.03 mol) triethylamin in 50 mL dried THF was treated in a drop wise manner with a solution of 2.8 g (0.02 mol) dimethylvinyl chlorosilane in 10 mL of THF under argon, at room temperature. After (8 h) stirring at room temperature the reaction mixture was filtered. The THF was removed under reduced pressure to produce a nearly colorless oily residue. The residue was chromatographed over silica gel by CH_2Cl_2 to yield (50%) of DMVS.

IR (neat): ν = 1253 (C—Si) cm^{-1}, 1407 (C=C)cm^{-1}, 1739 (C=O) cm^{-1}, 2930 (aliphatic C—H) cm^{-1}.

^{1}H-NMR ($CDCl_3$)δ = 0.18 (s,6H, $SiCH_3$), 1.92 (s, 3H, CH_3), 3.81 (t,2H, CH_2O), 4.20 (t, 2H, CH_2OCO), 5.55 (m, 1H, SiCH=), 5.71 (d, 1H, CH_2=),6.05 (d, 1H, CH_2=), 6.10 (d, 2H, =CH_2) ppm.

^{13}C-NMR ($CDCl_3$)δ = −1.82($SiCH_3$), 18.68(CH_3), 61.27(CH_2O), 66.13(CH_2OCO), 125.9(SiCH=), 133.8(CH2=), 136.6(CH2=),137.3(CH3—C=),167.6(C=O) ppm.

Other sily monomers 2-[(triethylsilyl)oxy] ethyl methacrylate (TESiEMA), 2-((*tert*-butyldimethylsilyl)oxy)ethyl methacrylate (TBSiEMA), and 2-((triphenylsilyl)oxy)ethyl methacrylate (TPhSiEMA) were synthesized by same procedure as described in reference.[26]

Crosslink copolymers preparation

Crosslink copolymers were prepared by bulk free-radical copolymerization. The mixture of silyl monomers of HEMA ester (TESiEMA, TPhSiEMA), monomer A, with different molar ratio of HEMA and MAA (monomer B) specific mol presents of DMVS (5 and 10%) and using AIBN as initiator ([*I*] = 0.01*M*), were frozen and degassed under vacuum. The freezing and degassing procedure were repeated three times, and the ampoules were sealed. The solution was polymerized at 60–70°C for 48 h. Then

TABLE II
The Molar Composition of pH-Sensitive Hydrogels

Hydrogel	TBSiEMA : MAA : %CA	Hydrogel	TESiEMA : MAA : %CA
H_1	1 : 1 : 5%	H_4	1 : 1 : 5%
H_2	1 : 3 : 5%	H_5	1 : 3 : 5%
H_3	3 : 1 : 5%	H_6	3 : 1 : 5%

the viscous solution was poured from the ampoule in to cold methanol, the precipitate was separated, and washed several times with methanol, dried under vacuum at room temperature to give products. In the copolymer preparation, the total monomer concentration, Monomer A/Monomer B mole ratio, crosslinker concentrations were changed. The conditions for the production of hydrogels are summarized in Table I.

General procedure for synthesis of pH-sensitive hydrogels

In pyrex glass ampoules, the mixture of monomers substituted with siloxyl group (TESiEMA, TBSiEMA) with MAA in different molar ratio and specific mol presents of DMVS (5%) were polymerized at 60–70°C in the oil bath using AIBN (0.01*M*) as initiator. After the specified time (72 h), the precipitated network polymer was collected, washed with methanol, and dried in vacuum. The conditions for the production of pH-sensitive hydrogels are summarized in Table II.

Drug loading in hydrogels

Seventy milligrams of hydrogels (H_1, ..., H_6) were placed to 10 mL of MZ to suck up the total amount of the drug solution. After $\sim$ 60 min, the completely swollen hydrogels loaded with MZ were washed with deionized water and placed in desiccators and dried under vacuum at room temperature.

Determination of drug entrappedamount

The amount of drug entrapped in the hydrogels was determined by an indirect method. After the gel preparation, the washing with methanol was collected and tested using UV–vis spectroscopy. The difference between the amount of drug initial drug and that of the drug in the washing is taken as an indication of the amount of drug entrapped.

In vitro release studies

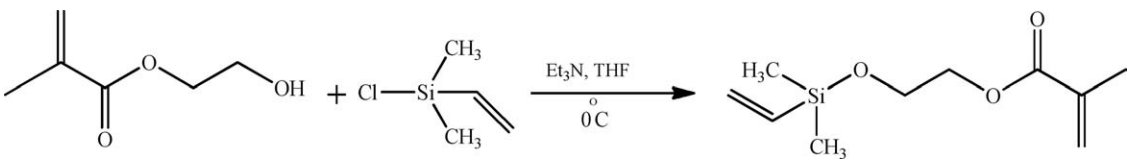
The copolymers (10 mg) were poured into 3 mL of aqueous buffer solution (SGF: pH 1 or SIF: pH 7.4). The mixture was introduced into a cellophane membrane dialysis bag. The bags was closed and transferred to a flask containing 20 mL of the same solution maintained at 37°C. The external solution was continuously stirred, and 3 mL samples were removed at selected intervals. The volume removed was replaced with SGF or SIF. The sample of hydrolyzate was analyzed by UV spectrophotometer.

RESULTS AND DISCUSSION

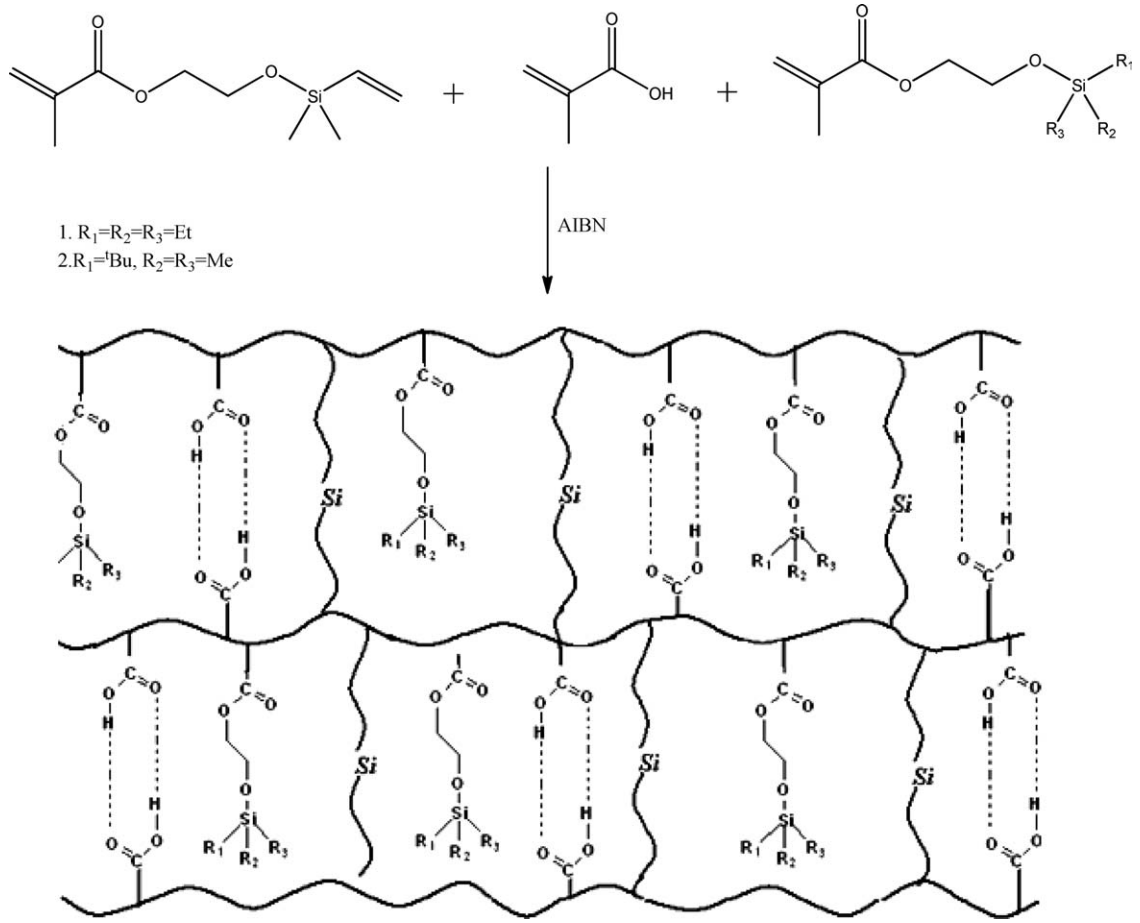
Crosslinking agent was synthesized by reaction of chlorodimethyl vinylsilane with HEMA in the presence of Et_3N in THF at room temperature to produce 2-((dimethyl(vinyl)silyl)oxy)ethyl methacrylate (DMVS) Scheme 1.

This compound was simply purified and identified by spectroscopic method. Then it was reacted with several ratios of other monomers to produce crosslinked polymers. For synthesis of network polymers, we used different siloxy derivatives of HEMA (Table I). Triethylsiloxy and triphenylsiloxy derivatives were synthesized by reaction of HEMA with Et_3SiCl and Ph_3SiCl in same reaction to produce 2-[(triethylsilyl)oxy] ethyl methacrylate (TESiEMA) and 2-(triphenylsilyl)oxy)ethyl methacrylate (TPhSiEMA). These siloxy derivatives were copolymerized with HEMA and crosslinking reagent (DMVS) with ratio of 5 and 10%, respectively. In the other reaction, we used different ratio of these monomers in network polymer.

Differential scanning calorimeter (DSC) was evaluated. The glass transition temperature (T_g) was determined from the DSC thermograms. The values are given in Table I. It appears that with increasing crosslinking degree, which would decrease the flexibility of the chains and the ability of the chains to undergo segmental motion, which would increase the T_g values. The T_g value of the copolymers with 10% of crosslink agent would be higher than T_g value of the copolymer copolymers with 5% of crosslink agent. Also the T_g value in the copolymer



Scheme 1 Synthesis of 2-((dimethyl(vinyl)silyl)oxy)ethyl methacrylate.



Scheme 2 Preparation of crosslinked copolymer containing siloxyl groups.

P_3, with higher content of triethylsilyl derivative of HEMA (TESiEMA) with respect to HEMA monomer (i.e., ratio of 2 : 1), is substantially reduced. The silyl group as a plasticizer increases the flexibility of hard polymers and reduces its T_g. It seems that incorporation of more silyl groups in side chains of polymer

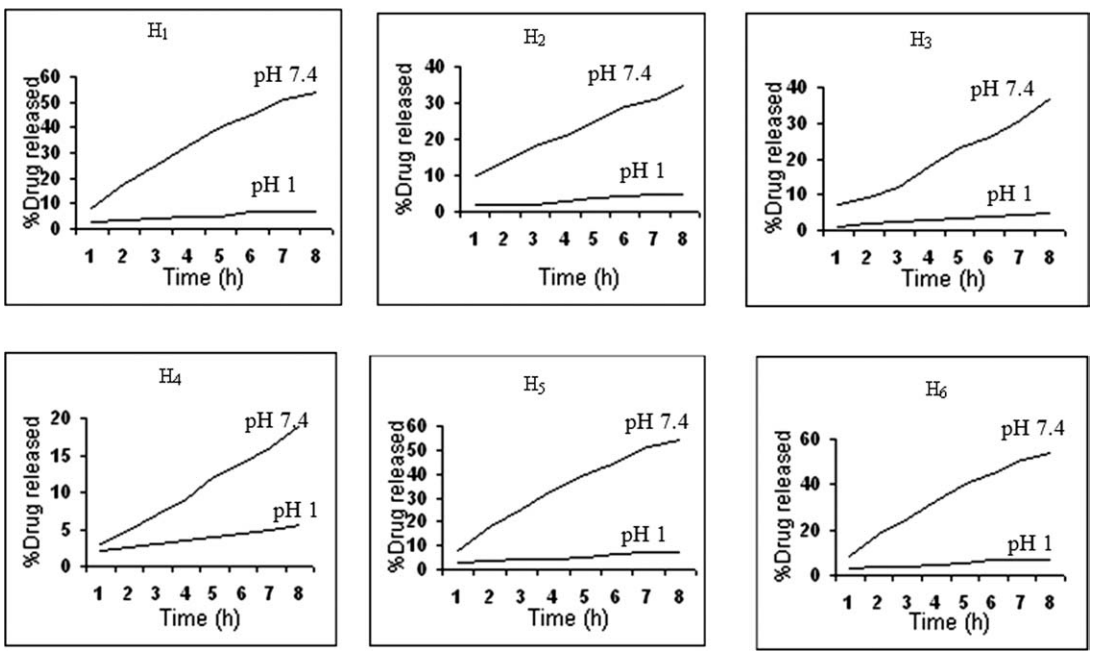


Figure 1 Release data of MZ from polymeric carriers as a function of time at 37°C.

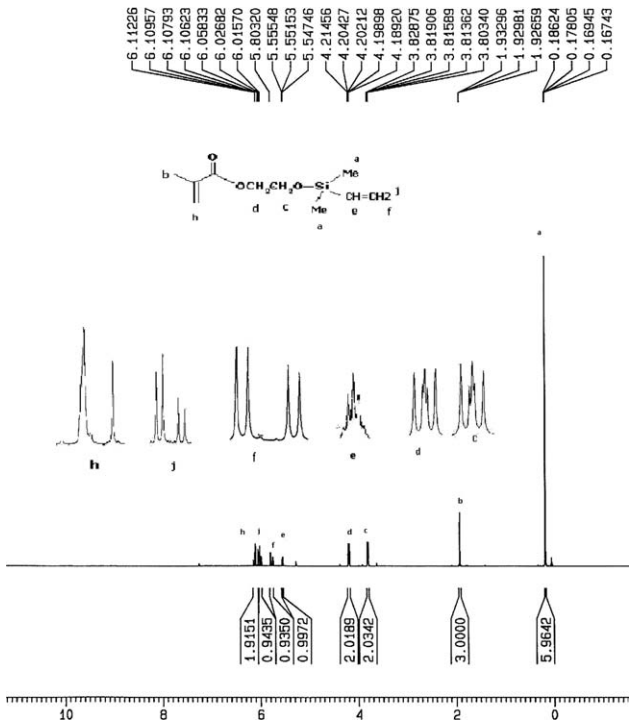


Figure 2 ^{1}H-NMR spectrum of 2-((dimethyl(vinyl)silyl)oxy)ethyl methacrylate (DMVS).

reduces the intermolecular interaction of chains and T_g value is reduced. In this way with synthesis of new crosslinking reagent in the base of silyl group (vinylsilane), we prepared new crosslinking copolymers and studied them. Incorporation of silyl group in polymer network was previously done only by hydrosilylation of silyl polymers to double bounds. Therefore, by application of this new route, it is possible to prepare novel network polymers without using hydrosilylation reaction.

Design and synthesis of new terpolymeric hydrogel systems based on silyl monomers was other objective in our study (Scheme 2). Incorporation of silyl groups into the polymer structure creates macromolecule with novel architecture that could be used as membranes for gas or fluid separation. These polymeric hydrogels containing hydrophilic constituents are expected to serve not only as membranes but also as drug delivery matrix for oral drug delivery. Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastrointestinal tract (GIT) presents several formidable barriers to drug delivery. To achieve successful colonic delivery, a drug needs to be protected from absorption of the environment of the upper GIT and then be abruptly released into the proximal colon, which is considered the optimum site for colon-targeted delivery of drugs. These requirements have prompted the development of polymeric systems that swell minimally under acidic conditions but extensively in basic intestinal medium. Colonic drugs delivery has gained increased importance not only for the delivery of the drugs for the treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides.[27] Silicone's

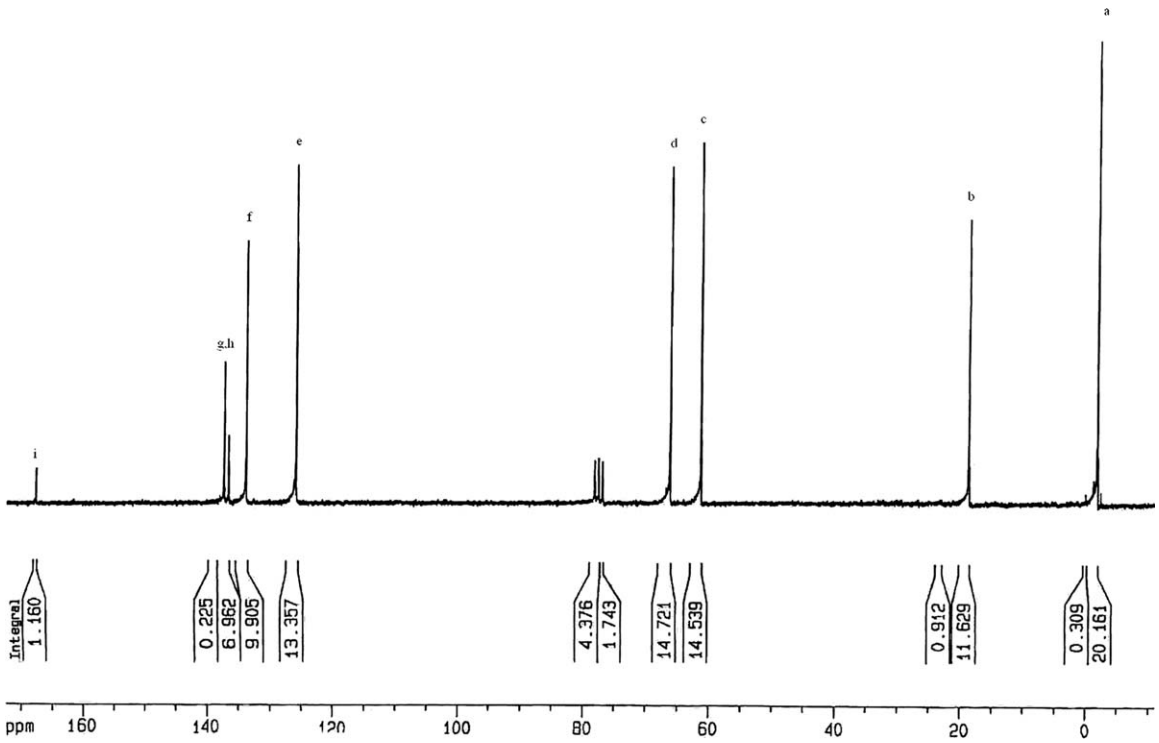


Figure 3 ^{13}C-NMR spectrum of 2-((dimethyl(vinyl)silyl)oxy)ethyl methacrylate (DMVS).

hydrophobicity makes it particularly suitable for the delivery of lipophilic drugs. Silicones generally are impermeable to polar compounds, which results in low permeability of water-soluble drugs. Drug release profiles from polymers of containing silicone are affected by the physiochemical properties of the drug and any additives used in the formulation, as well as the polymer geometry and the drug and additive loading. Silicone's hydrophobicity makes it particularly suitable for the delivery of lipophilic drugs.

As shown in Figure 1, an increase in the content of MAA in the feed monomer mixtures resulted in less swelling at pH 1 but greater swelling at pH 7.4. This is because the increase of MAA content in the hydrogels provides more hydrogen bonds at low pH and more electrostatic repulsion at high pH. Based on this rationale, we have synthesized new hydrogels containing different molar ratios of acidic monomers. Due to the great difference in swelling ratio at pH 1 and 7.4 polymer bonded drugs, candidates for colon-specific drug delivery (Fig. 1).

Characterization of monomers and polymers

Crosslinking agent of DMVS was identified by ^{1}H-NMR and ^{13}CNMR and IR spectroscopy. These data are given in experimental section for this compound. A typical spectrum of ^{1}H-NMR and ^{13}C-NMR are shown in Figures 2 and 3, respectively. Crosslink copolymers were characterized by infrared spectroscopy. The resulting network polymers swell and become soft if they are exposed to solvents such as H_2O and most other organic solvents without dissolving. In the FT-IR spectra, absorption of C-Si bond appeared in region of 1258–1270 and 837–900 cm^{-1}, which refers to stretching, and bending vibration respectively, absorption in 1730 cm^{-1} refers to stretching carbonyl bond in network polymers with silyl methacrylate linkage (TPhSiEMA, TESiEMA), absorption in 1710 cm^{-1} refers to carbonyl group of MAA, and absorption in 2500–3300 cm^{-1} is referring to OH bond in MAA. This way characterized presence of silyl groups, HEMA, and methacrylic acid in crosslinked copolymers.

CONCLUSIONS

In this study, we synthesized and identified novel organosilicon crosslinking reagent and network copolymers of HEMA ester and methacrylic acid by free radical polymerization. The DSC analysis indicated that the glass transition temperature of copolymer decreases with incorporation of silyl groups in side chains of polymer.

Therefore placing silyl groups and regulating the crosslinking degree can produce novel polymer systems with the new physical and chemical properties and applications. PH-sensitive hydrogels for colon-specific drug delivery system were synthesized, and influence of the hydrogels composition and pH value on the release of MZ at 37°C was investigated. The hydrolytic behavior of the hydrogels was dependent on the content of MAA groups, which caused a decrease in releasing of SGF or an increase in SIF.

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