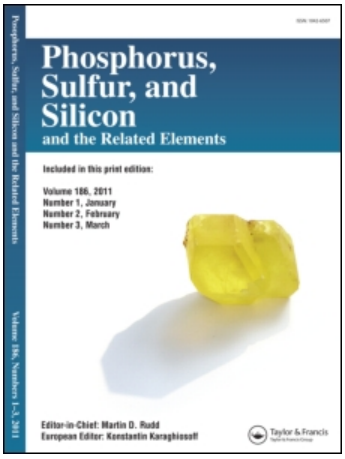

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NEW pH-SENSITIVE HYDROGELS FOR ORAL DELIVERY OF HYDROPHOBIC DRUGS

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A series of acrylic copolymers containing silyl pendant groups was prepared by free radical cross-linking copolymerization. Me_3Si, Et_3Si, and Ph_3Si together with cubane-1,4-dicarboxylic acid (CDA) were covalently linked with 2-hydroxyethyl methacrylate (HEMA). CDA linked to two HEMA group is the cross-linking agent (CA). Free radical cross-linking copolymerization of the methacrylic acid (MAA) and organosilyl monomers with two different molar ratios of CA was carried out at 60–70°C. The compositions of the cross-linked three-dimensional polymers were determined by FT-IR spectroscopy. The glass transition temperature of the network polymers was determined calorimetrically. Equilibrium swelling studies were carried out in enzyme-free simulated gastric and intestinal fluids (SGF and SIF, respectively). A model hydrophobic drug, the steroid hormone estradiol, was entrapped in these gels, and the in vitro release profiles were established separately in both SGF (pH 1) and SIF (pH 7.4). Incorporation of silyl groups in a new macromolecule system modified network polymers for drug delivery.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Estradiol; hydrogel; hydrophobic drug; oral drug delivery; pH-sensitive

INTRODUCTION

Drug delivery technology is evolving through the creation of new techniques that deliver a variety of drugs effectively. These developments benefit numerous patients by achieving a higher patient compliance and quality of life. Hydrogels consist of three-dimensional polymeric networks with excellent water-absorbing capacity and biocompatibility.[1,2] Depending on their formulation, hydrogels can exhibit a variety of drug release profiles determined by the release environment. Thermosensitive and pH-sensitive hydrogels are the most extensively studied gels because of their controlled-release characteristics.[3–5] The release of large protein drugs such as insulin from hydrogels is of great interest, because these high molecular weight drugs are normally delivered to the body through injections, with low patient compliance.[6] Hydrogels, which have great swelling capacity, can entrap

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these high molecular weight drugs and thus release them in a controlled fashion.[7] Although hydrogels appear to work well with large hydrophilic proteins such as insulin,[8–10] their use for the release of hydrophobic drugs has not been well studied. Like protein drugs, when taken orally, hydrophobic drugs such as estradiol are greatly degraded by the digestive enzymes, thus losing any therapeutic effects. A pH-sensitive hydrogel that characteristically releases at a high pH could protect estrogen in the low pH acidity of the stomach and thus release the drug in the more stable and basic environment of the intestine. Estradiol, a hydrophobic steroid, represents an important hormone to the female reproductive system.

The presence of polar functional groups such as carboxylic acid is needed for pH-sensitive properties of polymers, but such polar functionality reduces hydrophobic drug loading.

Since most of drug molecules have a lipophilic structure, the presence of lipophilic groups on the polymer increases drug lading, however, the presence of lipophilic groups decreases the diffusion of hydrolyzing agents to the polymer to deliver the drug.

The presence of hydrophilic groups on polymers decreases drug loading on polymers, while the rate of release is increased. Hence to reach an ideal system, there must be a suitable balance between lipophilicity and hydrophilicity. The silyl groups have lipophilic properties; therefore the synthesis of silyl derivative of polymers and copolymers could be important in oral delivery of hydrophobic drugs.

In this article, we report the synthesis and properties of methacrylate copolymers modified with Me_3Si, Et_3Si, and Ph_3Si groups. The methacryloyloxyethyl esters of Me_3Si (TMSiEMA), Et_3Si (TESiEMA), Ph_3Si (TPhSiMA), and cubane-1,4-dicarboxylic acids were prepared as polymerizable silyl monomers and cross-linking agents (CA), respectively. Free radical cross-linking copolymerization of the resulting monomers with methacrylic acid (MAA) in the various CA ratios produced silyl pendent network polymers. The DSC analysis showed that the attaching of a silyl group in the copolymer reduces the value of the glass transition temperature (T_g). A model hydrophobic drug was entrapped in these gels, and the in vitro release profiles were established separately in both simulated gastric fluids (SGF, pH 1) and simulated intestinal fluids (SIF, pH 7.4). The influence of different factors, such as amounts of silane monomers, on the swelling and drug-released behaviors were studied.

RESULTS AND DISCUSSION

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 biocompatibility. Silicones, or silicon polymers, have a number of advantages for use in medical devices and drug delivery systems.[11,12] Silicone's hydrophobicity makes it particularly suitable for the delivery of lipophilic drugs.[13,14]

The study of swelling shows that swelling of hydrogels increases with time, first rapidly and then slowly, reaching a maximum constant swelling (mass equilibrium swelling, MES). In all cases, the swelling weight reached an equilibrium after 5 h. The equilibrium swelling ratio of the hydrogels was a function of the network structure, crosslinking ratio, hydrophilicity, and degree of ionization of the functional groups. An increase in the content of MAA in the feed monomer mixtures resulted in less swelling in SGF but greater swelling in SIF. The results showed that, because of the hydrophobicity of the silyl group, the more

silane monomers in the copolymeric hydrogels, the lower was the swelling ratio of the gels. On the other hand, with increased cross-linking, diffusion of hydrolyzing agents in the polymer network is reduced, and the release rate is slower.

The values of entrapped drug in the hydrogel are given in Table S2 (available online in the Supplemental Materials). Due to the great difference in the swelling ratio at pH values of 1 and 7.4 and suitable drug loading for P-3, P-7, and P-11, these polymers appear to be good candidates for colon-specific hydrophobic drug delivery.[12,15]

In Vitro Release of Estradiol

The degree of release of the hydrogels containing estradiol as a function of time is shown in Figure S1 (Supplemental Materials). The order of releases in this series was significantly affected by polymer composition. As the content of MAA in the feed monomers increased, the release rate decreased at pH 1 but increased at pH 7.4. The existence of hydrogen-bonding interactions between –COOH groups in the polymer matrix results in a complex structure within the network, and so the movement of polymeric segments is restricted. This also accounts for minimum releases of the gel in a medium of pH 1. However, when the sample is placed in a medium of pH 7.4, the almost complete ionization of –COOH groups present within the polymer network not only increases the ion osmotic swelling pressure to a great extent but also enhances the relaxation of macromolecular chains because of repulsion among similarly charged $–COO^-$ groups.

The large silyl group resulted in less collapsed networks at low pH. This led to a relatively large pore size of the networks. Thus, drugs could diffuse readily from the gel at low pH.

CONCLUSIONS

The most useful pH-sensitive polymers swell at high pH values and collapse at low pH values, and the triggered drug delivery occurs upon an increase in the pH of the environment. Such materials are ideal for systems such as oral delivery, in which the drug is not released at low pH values in the stomach but rather at high pH values in the upper small intestine. The silyl copolymers with different contents of MAA and CA were synthesized by free radical cross-linked copolymerization. By placing lipophilic silyl groups in pH-sensitive hydrogel and regulating the cross-linking degree, we can obtain novel pH-sensitive polymer systems with novel physical and chemical properties and new applications. These pH-sensitive polymer systems with high content of silyl side chain substituents can be used as oral delivery of hydrophobic drugs.

EXPERIMENTAL

Synthesis of monomers and copolymerization were carried out under dry argon to exclude oxygen and moisture from the reaction systems.

Materials

Cubane-1,4-bis(methacryloyloxyethyl) carboxylate (CA)[16] and organosilyl monomers[17] were prepared by the methods described in the literature. Estradiol was purchased from Sigma-Aldrich Co. The solvents and reagents were purchased from Merck and

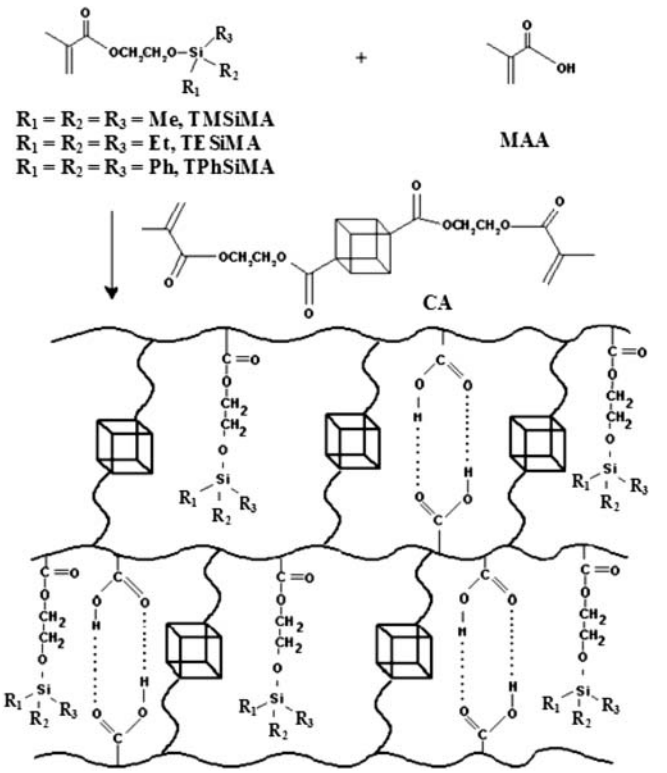
Fluka Co. Et_3SiCl, Me_3SiCl, and Ph_3SiCl were used as received. The initiator of 2,2′-azaobis(isobutyronitrile) (AIBN) was purified by crystallization from methanol.

Measurements

The infrared spectra were recorded on a Shimadzu FT IR-408 spectrophotometer. The differential scanning calorimetry curves were obtained on a TGA/SDTA 851 calorimeter at heating and cooling rates of 10°C/min under N_2. The amount of released drug was determined on a Philips PU 8620 ultraviolet spectrophotometer at the absorption maximum of the free drug ($\lambda_{max} = 280$ nm) using a 1 cm quartz cell.

Crosslinked Copolymerization

In Pyrex glass ampoules, mixtures of resulting silyl monomers with MAA in different molar ratios and specific mol percents of CA (5% and 10%) were polymerized at 60–70°C in a thermostated water bath, using 2,2′-azaobis(isobutyronitrile) (AIBN) as initiator ([I] = 0.02 M) and dried dioxane as solvent ([M] = 1.0 M). After the desired time (48 h), the precipitated hydrogels was collected and washed with methanol for 1 day, while the methanol was changed every 4 h in order to remove any unreacted monomers. After washing, the samples were dried in air and stored in desiccators until use (Scheme 1). In



Scheme 1 Preparation of pH-sensitive hydrogels containing silyl group.

the FT-IR spectra, absorption of C–Si bond appeared in regions of 1258–1270 and 837–900 cm^{-1}, which refers to stretching and bending vibration, respectively.

Buffer Solutions

Enzyme-free SGF (pH 1) and SIF (pH 7.4) were prepared according to the method described in the U.S. Pharmacopeial Convention.[18] To overcome the hydrophobicity of estradiol, the buffers for estradiol were modified by adding ethanol (10%, v/v), because estradiol is highly soluble in ethanol. The pH change due to the addition of ethanol was corrected with either 1.0 N HCl or 1.0 N NaOH and then used for the drug loading, swelling, and drug release experiments.

Thermal Behavior

In general, polymers having low glass transition temperature show high diffusion coefficients for small molecules, but polymers having high glass transition temperature exhibit a considerably higher permaselectivity. The glass transition temperature (T_g) was determined from the DSC thermograms. The values are given in Table S1 (Supplemental Materials). It appears that with an increased degree of cross-linking, the flexibility of the chains and the ability of the chains to undergo segmental motion decreased, which would then increase the T_g values.[16] The silyl group not only reduced the internal hydrogen bonds between the polymer chains, but also functioned as a plasticizer increasing the flexibility of the hard polymers and reducing the T_g value.

Swelling Ratio

To measure the swelling, preweighed dry drug-free hydrogels were immersed in various buffer solutions (pH 7.4 and pH 1) at 37°C. After excess buffer solution on the surface was removed with filter paper, the weight of the swollen samples was measured at various time intervals. The procedure was repeated until there was no further weight increase. The degree of swelling was calculated according to the following relationship:

$$SW\,(\%) = [(W_s - W_d)/W_d] \times 100$$

where, W_s and W_d represent the weight of swollen and dry samples, respectively. Time-dependent swelling behaviors of cross-linked polymers in pH 1 and pH 7.4 at 37°C are given in Table S2 (Supplemental Materials).

Drug Loading in Hydrogels

First, 50 mg of each hydrogels were placed in 10 mL of solution containing 5 mg of estradiol to suck up the total amount of the estradiol solution. After approximately 120 min, the completely swollen hydrogels loaded with estradiol were placed in desiccators and dried under vacuum at room temperature.

Amount of Drug Entrapped

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 initially employed and the drug content in the washing was taken as an indication of the amount of drug entrapped. The values of quantification of entrapped drug in the hydrogel based on the total amount are given in Table S2 (Supplemental Materials).

In Vitro Release Studies

The copolymers (10 mg) were poured into 3 mL of simulated gastric fluid (SGF) in pH of 1 or simulated intestinal fluid (SIF) in pH of 7.4. The mixture was introduced into a cellophane membrane dialysis bag. The bags were 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 hydrolyzed sample was analyzed by UV spectroscopy ($\lambda_{max} = 280$ nm).

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