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Fabrication of Size-Controllable mPEG-Decorated Microparticles Conjugating Optically Active Ketoprofen Based on Self-Assembly of Amphiphilic Random Copolymers

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ABSTRACT: Novel size-controllable mPEG-decorated polymeric microparticles binding optically active ketoprofen were successfully fabricated based on chemoenzymatic synthesis and self-assembly of amphiphilic random polymer–ketoprofen conjugates with mPEG and (*S*)-ketoprofen as pendants. A series of $mPEG_{350}$- or $mPEG_{1000}$-functionalized amphiphilic random polymer–ketoprofen conjugates with drug loading capacity from 16.5% to 73.2% were easily prepared by combining enzymatic resolution with radical polymerization and characterized by Fourier Transform Infrared spectroscopy, ^{1}H-NMR, and gel permeation chromatography. The formation of aggregates from the amphiphilic random polymer–ketoprofen conjugates was investigated by ultraviolet-visible absorption spectra using pyrene as the guest molecule. Transmission electron microscopy measurement revealed that the self-assemblies were well dispersed as spherical microparticles. The size of the self-assemblies could be widely tuned by varying the length of mPEG chains and the content of ketoprofen in the synthetic polymer–ketoprofen conjugates, and a series of mPEG-decorated (*S*)-ketoprofen-bound polymeric microparticles with average radius from 70 nm to 1.1 μm were obtained. The successful preparation of the microparticles containing (*S*)-ketoprofen provided a new strategy for the design and fabrication of optically active drug delivery systems. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2012

KEYWORDS: drug delivery systems; microparticles; radical polymerization; self-assembly; (*S*)-ketoprofen

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INTRODUCTION

In recent years, the design and fabrication of micro/nanostructures based on self-assembly of amphiphilic polymer–drug conjugates have attracted increasing attention as these drug delivery systems offer numerous advantages including improved stability, prolonged circulation in the blood, and enhanced accumulation in tumor tissue.[1–7] Especially, introducing biocompatible PEG chains on surface of the micro/nanostructures could prevent the unspecific protein adsorption and cell adhesion, and thus further prolongs circulation time of these systems and enhances the pharmacological effect of given drugs.[8–10] However, most studies about these polymeric micro/nanostructures were focused on highly regular molecules such as amphiphilic block copolymers. Few reports about the formation of micro/nanoparticles through the directed-assembly of amphiphilic random polymer–drug conjugates were available.[11] Ketoprofen is an important nonsteroidal anti-inflammatory drugs that has been widely used for musculoskeletal and joint disorders.[12–14] However, ketoprofen has rather short plasma half-life, and its long term used could cause gastrointestinal ulceration and hemorrhage.[15–17] Moreover, the anti-inflammatory activity of ketoprofen is mainly due to its (*S*)-enantiomer, while the (*R*)-one has a very poor activity and, even in some case, has unwanted physiological side effects and toxicity.[18–20] To improve the therapeutic index, some drug delivery systems of ketoprofen have been developed.[21–28] However, few reports about the micro/nanostructures self-assembled from polymer–ketoprofen conjugates for drug delivery were available. Moreover, ketoprofen connected to polymer carriers was still racemic mixtures in most of the reported polymer–ketoprofen conjugates. The reported polymer–ketoprofen conjugates were mostly obtained by conventionally chemical methods, which led to the lack of enantioselectivity. Enzymes, as environmentally friendly biocatalysts, play an important role in the production of optically active compounds due to the high enantioselectivity and mild reaction conditions.[29–31] In previous work, we reported the synthesis of

(*S*)-ketoprofen vinyl ester by the irreversible enzymatic resolution of racemic ketoprofen vinyl ester[32] and further prepared optically active polymeric prodrug of ketoprofen by the radical copolymerization of resultant (*S*)-ketoprofen vinyl ester with methyl methacrylate.[33]

Herein, we wish to achieve the formation of mPEG-decorated (*S*)-ketoprofen-bound microparticles based on the chemoenzymatic synthesis and self-assembly of amphiphilic random polymer–ketoprofen conjugates. First, a series of amphiphilic random polymer–ketoprofen conjugates with mPEG chains and (*S*)-ketoprofen as pendants were prepared by chemoenzymatic synthetic route. Then, the formation of self-assemblies from the polymer–ketoprofen conjugates was investigated by ultraviolet-visible (UV-vis) spectroscopy. The aggregation morphologies and size distribution of the self-assemblies were characterized by transmission electron microscopy (TEM) and dynamic light scattering (DLS), respectively. Finally, the effect of copolymer composition including mPEG chain length and ketoprofen content on the size of self-assemblies was investigated, and a series of mPEG-decorated (*S*)-ketoprofen-bound microparticles with controllable size were obtained.

EXPERIMENTAL

Materials and Instruments

Lipozyme® immobilized from Mucor miehei (Lipozyme®) was purchased from Fluka (Switzerland). Racemic and optically pure ketoprofen [2-(3-benzoylphenyl) propionic acid] were obtained from Zhejiang Jiuzhou Pharmaceutical Co. (Taizhou, P.R. China). Racemic ketoprofen vinyl ester was prepared and purified according to the literature.[34] Polyethylene glycol monomethylether, 350 ($mPEG_{350}$, number-average molecular weight M_n = 350 g mol^{-1}) was purchased from Alfa Aesar (USA). Polyethylene glycol 1000 monomethylether ($mPEG_{1000}$, number-average molecular weight M_n = 1000 g mol^{-1}) was purchased from Fluka (Switzerland). The corresponding mPEG methylacrylates ($MPEG_{350}$, $MPEG_{1000}$) were synthesized by the condensation reaction of mPEG with methacrylic acid and purified as described by Yildiz et al.[35] α,α'-Azobis-(isobutyronitrile) (AIBN) was purified by recrystallization in ethanol and dried at room temperature under vacuum. All other chemicals used in this work were of analytical grade.

Fourier Transform Infrared (FTIR) spectra were measured on a Nicolet Nexus FTIR 670 spectrophotometer at room temperature. ^{1}H-NMR spectra were recorded on a Bruker AMX-400 MHz spectrometer using tetramethylsilane as an internal standard. The enantiomer of ketoprofen was analyzed by HPLC using an Agilent 1100 series with a chiral column [(*S,S*)-Whelk-O1, 250 × 4.6 mm, Regis] and a UV detector (250 nm). Gel permeation chromatography (GPC) was performed with a system equipped with refractive-index detector (Waters 2410) and Waters Styragel columns. The GPC columns were standardized with narrow dispersity polystyrene in molecular weights ranging from 4.7 × 10^6 to 2000, and tetrahydrofuran was used as the mobile phase.

Synthesis of (*S*)-Ketoprofen Vinyl Ester

(*S*)-ketoprofen vinyl ester (*S*-KVE) was synthesized and purified according to the literature reported by our laboratory.[31] The reaction was initiated by adding Lipozyme® (150 mg) into a conical flask containing 15 mL dioxane/water (97.5/2.5, v/v) mixture solvent and 1.5 g racemic ketoprofen vinyl ester. The suspension was then kept at 25°C and shaken under 200 rpm. The reaction process was monitored by HPLC and terminated by filtering off the enzyme. The filtrate was evaporated under reduced pressure, and the product was separated by silica gel chromatography with a mobile phase consisting of petroleum ether/ethyl acetate (30/1, v/v) to give light yellow liquid. ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.81–7.44 (9H, ArH), 7.26 (1H, —CH=), 4.87, 4.58 (2H, CH_2=), 3.86 (1H, CH—C=O), 1.57 (3H, —CH_3). ee ≈ 90%.

Synthesis of Poly[$MPEG_{350}$-*co*-(*S*-KVE)]

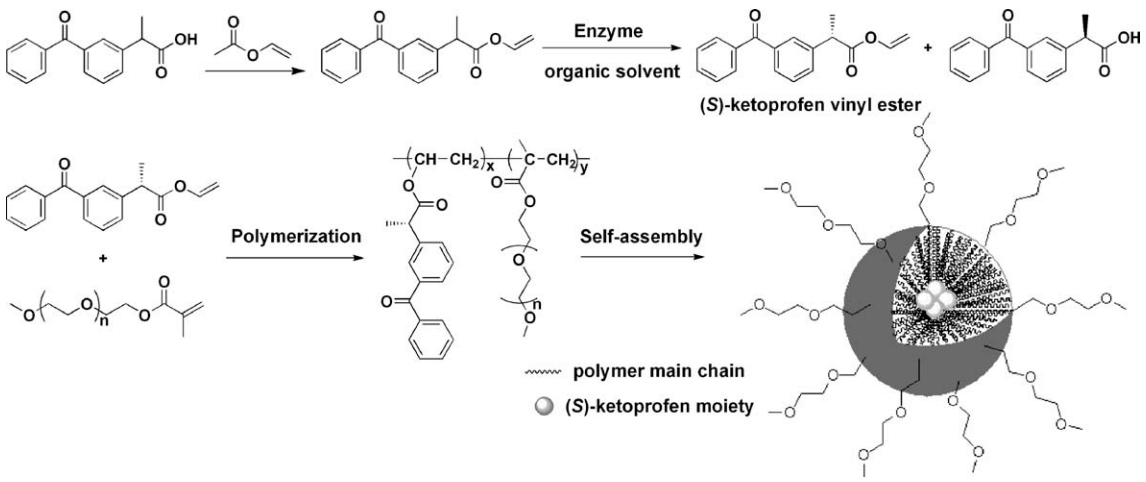
Poly[$MPEG_{350}$-*co*-(*S*-KVE)] was prepared by radical copolymerization of $MPEG_{350}$ with *S*-KVE using AIBN as initiator. The copolymerization was performed as follows: *S*-KVE and $MPEG_{350}$ were dissolved in dimethyl sulfoxide (DMSO), and AIBN was added as initiator. The mixture was degassed by three freeze-thaw cycles, and then stirred under nitrogen at 70°C for 6 h. The resultant product was repeatedly precipitated in methyl *tert*-butyl ether and dried under vacuum to afford a light yellow solid. By changing the feed molar ratio of $MPEG_{350}$ to *S*-KVE in the copolymerization, a series of $mPEG_{350}$-bound polymer–ketoprofen conjugates with different drug contents were obtained. IR (NaCl, cm^{-1}): 3061, 2875, 1732, 1660, 1597, 1580, 1448, 1283, 1137, 1109, 722. ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.81–7.24 (ArH of ketoprofen), 4.32–3.38 (CH—O of main chain; —CH_2—O and CH_3—O of mPEG; CH—C=O of ketoprofen), 2.42–0.78 (—CH_3 of ketoprofen; C—CH_3 and —CH_2— of main chain).

Synthesis of Poly[$MPEG_{1000}$-*co*-(*S*-KVE)]

Poly[$MPEG_{1000}$-*co*-(*S*-KVE)] was also synthesized by AIBN-initiated radical copolymerization of $MPEG_{1000}$ with *S*-KVE. The copolymerization was performed by the similar procedures to give a light yellow solid. By changing the feed molar ratio of $MPEG_{1000}$ to *S*-KVE in the copolymerization, a series of $mPEG_{1000}$-connected polymer–ketoprofen conjugates with different drug contents were obtained. IR (NaCl, cm^{-1}): 3060, 2874, 1732, 1659, 1597, 1449, 1285, 1107, 723. ^{1}H-NMR ($CDCl_3$, δ, ppm): 7.82–7.20 (ArH of ketoprofen), 4.22–3.38 (CH—O of main chain; —CH_2—O and CH_3—O of mPEG; CH—C=O of ketoprofen), 2.42–0.75 (—CH_3 of ketoprofen; C—CH_3 and —CH_2— of main chain).

UV Measurement of Pyrene/poly[MPEG-*co*-(*S*-KVE)]

Self-assembly of the resultant mPEG-functionalized (*S*)-ketoprofen-conjugated amphiphilic copolymers poly[MPEG-*co*-(*S*-KVE)] was preliminarily proved by UV-vis absorption spectra, which were recorded on an Analytikjena SPECORD 200 UV-vis spectrophotometer. Pyrene was used as the guest molecule. The sample was prepared by adding poly[MPEG-*co*-(*S*-KVE)] aqueous solution to the vial containing a known amount of pyrene. The resultant mixture was heated at 50°C for 2 h and then cooled overnight at room temperature. The final concentration of pyrene was 10^{-4} M. For the control, instead of the polymer solution water was added. The polymer aqueous solution without pyrene was also chosen as a control. The absorption spectra were recorded ranging from 300 to 500 nm.



Scheme 1. Preparation of mPEG-decorated (*S*)-ketoprofen-bound polymeric microparticles.

Preparation of mPEG-Decorated (*S*)-Ketoprofen-Bound Microparticles

The synthetic amphiphilic polymer–ketoprofen conjugates with mPEG and (*S*)-ketoprofen as pendants were, respectively, dissolved in DMSO at an initial concentration of 0.05%. Then, a given volume of ultrapure water (10% of the solution) was added into the polymer/DMSO solutions with stirring. The resultant solutions were, respectively, dialyzed using dialysis bag (molecular weight cutoff (MWCO) = 3500 g mol^{-1}) against ultrapure water for 2 days to remove DMSO from the solutions.

TEM Measurement

TEM measurement was performed on a JEM 200CX instrument at an accelerating voltage of 100 kV. A drop of the sample solution was placed on a copper grid coated with carbon film and dried at atmospheric pressure and room temperature before measurement.

DLS Measurement

DLS measurement was performed on a Nanoseries (Malvern, UK) zetasizer. The scattering angle used was 90°, and the temperature was fixed at 25°C.

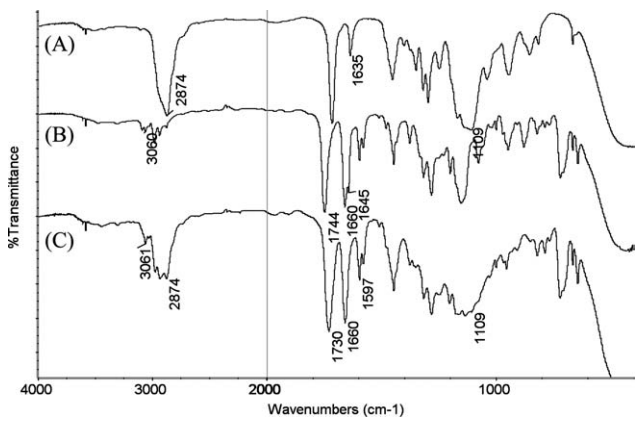


Figure 1. FTIR spectra of (A) $MPEG_{350}$, (B) (*S*)-ketoprofen vinyl ester (*S*-KVE), and (C) poly[$MPEG_{350}$-*co*-(*S*-KVE)].

RESULTS AND DISCUSSION

Synthesis and Characterization of Amphiphilic Polymer–Ketoprofen Conjugates with mPEG and (*S*)-Ketoprofen as Pendants

In this study, we developed a facile and effective method for the fabrication of mPEG-decorated optically active drug-bound polymeric microparticles based on chemoenzymatic synthesis and self-assembly of the amphiphilic random polymer–drug conjugates. The amphiphilic random polymers with mPEG and optically active drug as pendants were easily prepared by combining enzymatic resolution with radical polymerization. The entire synthetic route is shown in Scheme 1. Ketoprofen was chosen as a model drug. (*S*)-ketoprofen vinyl ester was first obtained by Lipozyme®-catalyzed hydrolysis of racemic ketoprofen vinyl ester in dioxane/water mixture solvent and then was

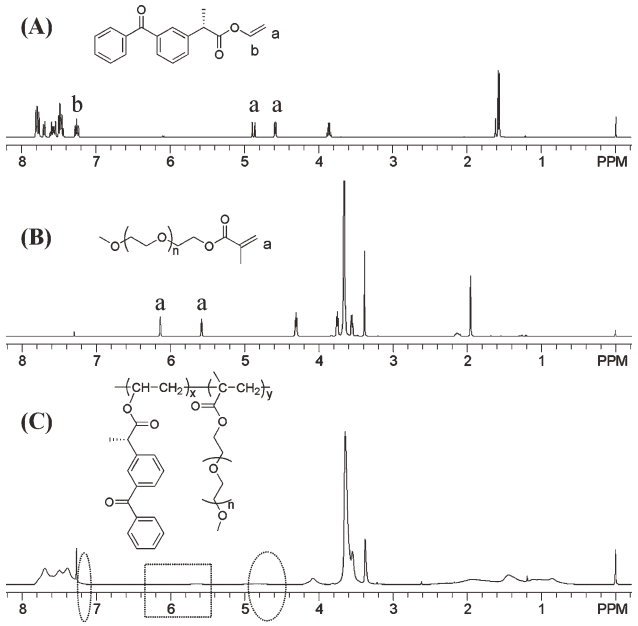


Figure 2. ^{1}H-NMR spectra of (A) (*S*)-ketoprofen vinyl ester (*S*-KVE), (B) $MPEG_{350}$, and (C) poly[$MPEG_{350}$-*co*-(*S*-KVE)].

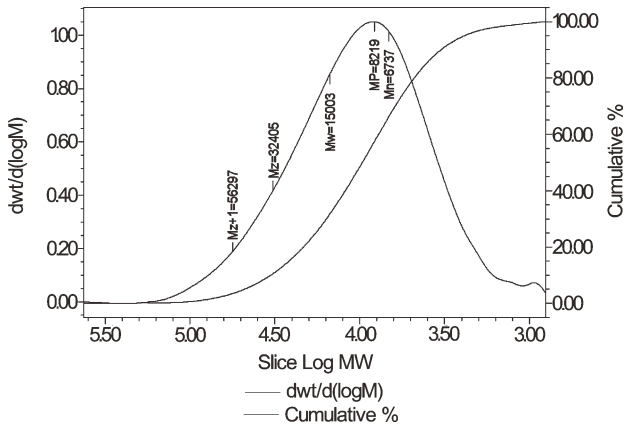


Figure 3. GPC distribution plot of poly[$MPEG_{350}$-*co*-(*S*-KVE)].

used as optically active drug monomer for the radical copolymerization with properly selected comonomers to provide (*S*)-ketoprofen-conjugated polymeric prodrugs with anticipate properties. Herein, two kinds of polymerizable mPEG methylacrylates ($MPEG_{350}$ and $MPEG_{1000}$) were, respectively, prepared as the comonomers for further polymerization because of notable advantages shown by mPEG in drug delivery systems such as well-defined biocompatibility, excellent hydrophilic nature, nontoxic and nonimmunogenic properties, and so on.

An amphiphilic random copolymer with $mPEG_{350}$ and optically active ketoprofen as pendants poly[$MPEG_{350}$-*co*-(*S*-KVE)] was first prepared by AIBN-initiated radical copolymerization of $MPEG_{350}$ with *S*-KVE and characterized by FTIR, ^{1}H-NMR, and GPC. Analysis of the FTIR and ^{1}H-NMR spectra preliminarily confirmed the successful preparation of the copolymer. In FTIR spectrum of $MPEG_{350}$ (Figure 1), the characteristic band at 1635 cm^{-1} was assigned to the C=C stretching vibration of methylacryloyl group. The characteristic band attributed to the C=C stretching vibration of vinyl ester group appeared at 1645 cm^{-1} in FTIR spectrum of *S*-KVE (Figure 1). As expected, the two bands were difficult to be observed in FTIR spectrum of the corresponding copolymer poly[$MPEG_{350}$-*co*-(*S*-KVE)] (Figure 1). ^{1}H-NMR data of the copolymer [Figure 2(C)] also revealed the disappearance of methylacryloyl group (δ 5.54, 6.10 ppm) existing in $MPEG_{350}$ [Figure 2(B)] and vinyl group (δ 4.58, 4.88 ppm) in *S*-KVE [Figure 2(A)], and the existence of mPEG and ketoprofen moieties. From ^{1}H-NMR spectrum of poly[$MPEG_{350}$-*co*-(*S*-KVE)], the molar ratio of $mPEG_{350}$ to ketoprofen in the resultant copolymer could be approximately calculated according to the ratio between the integral of CH_3—O of mPEG (δ 3.38 ppm) and the integral of ArH of ketoprofen (δ 7.81–7.24 ppm). Therefore, content of ketoprofen in the copolymer could be evaluated by this method. The molecular weight and polydispersity of poly[$MPEG_{350}$-*co*-(*S*-KVE)] were determined by GPC, and the result further confirmed achievement of the copolymerization (Figure 3). Then, a series of optically active ketoprofen-conjugated $mPEG_{350}$-bound amphiphilic random copolymers with different drug contents were synthesized by changing the feed ratio of two monomers in the copolymerization and were characterized by the similar methods. The results are shown in Table I.

The radical copolymerization of $MPEG_{1000}$ with *S*-KVE was also performed using AIBN as initiator in DMSO. The resultant amphiphilic random copolymer poly[$MPEG_{1000}$-*co*-(*S*-KVE)] was characterized by FTIR and ^{1}H-NMR, and the molecular weight and polydispersity were determined by GPC. From FTIR spectrum of the resultant copolymer, it could be found that the characteristic bands at 1637 and 1645 cm^{-1} assigned to the polymerizable C=C of $MPEG_{1000}$ and *S*-KVE were absent in the corresponding copolymer. The characteristic signals that were, respectively, assigned to the C—H stretching vibration of aromatic rings (3060 cm^{-1}), conjugated carbonyl group C=O stretching vibration of ketoprofen (1659 cm^{-1}), and C—O stretching vibration of mPEG (1107 cm^{-1}) could be observed in FTIR spectrum of the copolymer. ^{1}H-NMR data of the copolymer also showed that the characteristic proton signals (δ 6.10, 5.54, 4.88, 4.58 ppm) assigned to polymerizable groups of two monomers disappeared, and the proton signals attributed to mPEG (δ 3.81–3.38 ppm) and ketoprofen (δ 7.82–7.20 ppm) moieties still appeared. From ^{1}H-NMR spectrum of poly[-$MPEG_{1000}$-*co*-(*S*-KVE)], the molar ratio of $mPEG_{1000}$ to ketoprofen in the resultant copolymer could be approximately calculated. Thus, the loading capacity of ketoprofen in the copolymer could be estimated. By changing the feed ratio of *S*-KVE to $MPEG_{1000}$ in copolymerization, a series of optically active ketoprofen-conjugated $mPEG_{1000}$-bound amphiphilic random copolymers with different drug contents were synthesized. The results are shown in Table II.

Formation and Characterization of mPEG-Decorated (*S*)-Ketoprofen-Bound Polymeric Microparticles

The resultant optically active ketoprofen-connected polymer–drug conjugates were amphiphilic copolymers, which contained hydrophobic drug molecules and hydrophilic mPEG chains. Therefore, certain selective polar solvents such as water may trigger self-assembly of the copolymers. The hydrophobic components were preferred to be tucked in the interior of an assembly, and the hydrophilic parts were exposed to the bulk solvent (Scheme 1). If the amphiphilic polymer–ketoprofen conjugates do indeed form the core-shell self-assemblies in water, the copolymers should be capable of acting as microcontainers for apolar guest molecules in water. Formation of the self-assemblies was preliminarily proved by UV-vis absorption spectra using pyrene as the guest molecule.[36] Pyrene has a strong hydrophobic character, as could be discerned from the UV absorption spectrum of pyrene in water (10^{-4} M) (Figure 4).

Table I. Poly[$MPEG_{350}$-*co*-(*S*-KVE)] with Different Ketoprofen Contents

Molar ratio[a]	Drug content[b](%)	M_w[c](g mol^{-1})	M_w/M_n[c]
1/1	16.5	32,000	2.75
2/1	35.7	16,000	2.25
3/1	48.1	30,000	4.13
4/1	53.7	29,000	3.12
8/1	70.9	15,000	2.23

[a]The feed molar ratio of (*S*)-ketoprofen vinyl ester (*S*-KVE) to $MPEG_{350}$, [b]Content of ketoprofen in the resultant copolymer, [c]Determined using GPC.

Table II. Poly[MPEG$_{1000}$-*co*-(*S*-KVE)] with Different Ketoprofen Contents

Molar ratio[a]	Drug content[b](%)	M_w[c](g mol^{-1})	M_w/M_n[c]
3/1	36.1	9700	2.21
4/1	47.9	12,000	2.18
8/1	61.2	11,000	2.13
10/1	66.8	11,000	2.03
15/1	73.2	11,000	2.13

[a]The feed molar ratio of (*S*)-ketoprofen vinyl ester (*S*-KVE) to MPEG$_{1000}$, [b]Content of ketoprofen in the resultant copolymer, [c]Determined using GPC.

However, when 10^{-4} M pyrene was dispersed in aqueous solution of the amphiphilic polymer–ketoprofen conjugate poly[MPEG$_{350}$-*co*-(*S*-KVE)], an UV absorbance of 0.40 was observed at 351 nm. Similarly, an UV absorbance of 0.35 was investigated at 351 nm when 10^{-4} M pyrene was dispersed in aqueous solution of the copolymer poly[MPEG$_{1000}$-*co*-(*S*-KVE)] (Figure 4). The results showed that the amphiphilic polymer–ketoprofen conjugates could form self-assemblies and pyrene was transferred into hydrophobic environment of the self-assemblies.

The amphiphilic polymer–ketoprofen conjugates were then assembled by adding ultrapure water to the solutions of copolymers in DMSO. The resultant solutions were dialyzed against ultrapure water and DMSO was removed from the solutions. Morphologies of self-assemblies from the polymer–ketoprofen conjugates were investigated by TEM. Apparently, the self-assemblies were well dispersed as individual particles with regularly spherical shape in aqueous phase (Figure 5). The sizes of the self-assemblies were measured by DLS (Figure 6). The average hydrodynamic radiuses of the particles self-assembled from the two copolymers poly[MPEG$_{350}$-*co*-(*S*-KVE)] and poly[MPEG$_{1000}$-*co*-(*S*-KVE)] were about 619 and 141 nm, respectively.

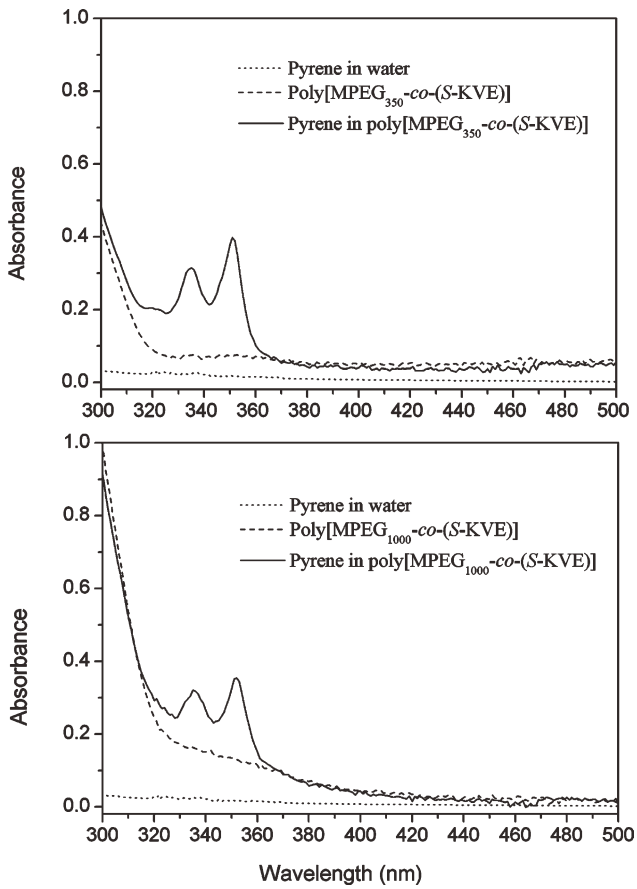


Figure 4. UV-vis spectra of pyrene in aqueous solutions of poly[MPEG-*co*-(*S*-KVE)], pyrene in water, and aqueous solutions of poly[MPEG-*co*-(*S*-KVE)].

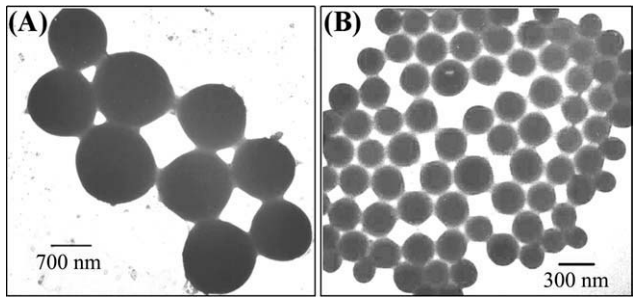


Figure 5. TEM images of the self-assemblies from (A) poly[MPEG$_{350}$-*co*-(*S*-KVE)] and (B) poly[MPEG$_{1000}$-*co*-(*S*-KVE)].

Size Control of mPEG-Decorated (*S*)-Ketoprofen-Bound Microparticles

The evident difference in size of the particles, respectively, self-assembled from poly[MPEG$_{350}$-*co*-(*S*-KVE)] and poly[MPEG$_{1000}$-*co*-(*S*-KVE)] led us to further investigate the effect of copolymer composition including mPEG chain length and ketoprofen content on the size of self-assemblies formed.

Polymer–ketoprofen conjugates binding mPEG$_{1000}$ chains were first chosen as objects to investigate the effect of ketoprofen content on the size of self-assemblies formed (Table III). It could be found that the mean radius of the self-assemblies decreased from 136 to 70 nm when the content of ketoprofen in the polymer–drug conjugates increased from 11.1% to 61.2%. However, the mean radius of the self-assemblies increased from 70 to 210 nm as the ketoprofen content further increased from 61.2% to 73.2%. The variation of aggregate size may be related to the repulsion of mPEG chains decorated on surface of self-assemblies and the hydrophobicity of ketoprofen

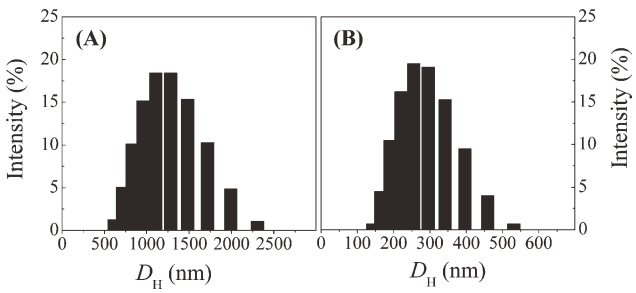


Figure 6. Size characterization of the self-assemblies from (A) poly[MPEG$_{350}$-*co*-(*S*-KVE)] and (B) poly[MPEG$_{1000}$-*co*-(*S*-KVE)] by DLS (D_H: hydrodynamic diameter).

Table III. Effect of Polymer Composition on Size of Self-Assemblies Formed

mPEG chain[a]	Drug content[b] (%)	Average radius[c] (nm)
$mPEG_{1000}$	11.1	136
$mPEG_{1000}$	47.9	124
$mPEG_{1000}$	61.2	70
$mPEG_{1000}$	66.8	141
$mPEG_{1000}$	73.2	210
$mPEG_{350}$	16.5	320
$mPEG_{350}$	35.7	470
$mPEG_{350}$	48.1	500
$mPEG_{350}$	53.7	530
$mPEG_{350}$	70.9	1100

[a]Length of mPEG chain in the resultant copolymer, [b]Content of ketoprofen in the resultant copolymer, [c]Determined by DLS.

moieties tucked in the interior of self-assemblies. When the content of ketoprofen in polymer–drug conjugates was very high, the hydrophobicity of the aggregate interior was greater, which led to an evident increase in final aggregate size.[37] while the ketoprofen content was very low, the content of mPEG chains was higher. Therefore, the repulsion of mPEG chains on surface of self-assemblies was greater, which also led to an increase in final aggregate size.

Polymer–ketoprofen conjugates binding $mPEG_{350}$ chains were then chosen as objects to further investigate the effect of ketoprofen content on the size of self-assemblies formed (Table III). We found that the mean radius of the self-assemblies increased from 320 nm to 1.1 μm as the content of ketoprofen in the polymer–drug conjugates increased from 16.5% to 70.9%. In these copolymers, the chain length of mPEG was shorter. Therefore, the repulsion of mPEG chains on surface of the self-assemblies was smaller. The hydrophobicity of ketoprofen became the main factor that affected the aggregate size. As the content of ketoprofen in the polymer–drug conjugates increased, the hydrophobicity of the aggregate interior increased, which led to a higher aggregation number of the copolymers and a significant increase in the final aggregate size.[36] Furthermore, the effect of mPEG chain length on the size of self-assemblies formed could be observed from Table III. When the content of ketoprofen connected the polymer carriers was similar, average radius of the self-assemblies from $mPEG_{1000}$-bound polymer–ketoprofen conjugates was smaller than that of the self-assemblies from $mPEG_{350}$-connected polymer–ketoprofen conjugates, which may be relative to the enhanced hydrophilic property of longer mPEG chains. By varying the length of linear mPEG chains and the content of ketoprofen in the polymer–ketoprofen conjugates, the size of the self-assemblies formed could be easily tuned and a series of mPEG-decorated (*S*)-ketoprofen-bound microparticles were obtained.

CONCLUSIONS

In this study, we developed a facile protocol for constructing mPEG-decorated (*S*)-ketoprofen-bound polymeric microparticles with tunable size based on chemoenzymatic synthesis and self-assembly of amphiphilic random polymer–drug conjugates with mPEG and optically active ketoprofen as pendants. The $mPEG_{350}$- or $mPEG_{1000}$-functionalized (*S*)-ketoprofen-connected polymer–drug conjugates were easily prepared by combining enzymatic resolution with radical polymerization, in which ketoprofen loading capacity was widely variable from 16.5% to 73.2%. The synthetic amphiphilic random polymer–ketoprofen conjugates could from core-shell-type self-assemblies and the aggregation morphology of the self-assemblies observed by TEM was regularly spherical shape. The size of the self-assemblies could be widely tuned from 140 nm to 2.2 μm by varying the length of linear mPEG chains and the content of ketoprofen in the polymer–drug conjugates. The resultant mPEG-decorated (*S*)-ketoprofen-bound polymeric microparticles were a novel potential drug delivery system. Further studies about the system are being conducted in our laboratory.

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