Novel Electrospun Nanofibers Incorporating Polymeric Prodrugs of Ketoprofen: Preparation, Characterization, and *In Vitro* Sustained Release

Jing Quan,[1,2] **Chengyao Wu,**[2] **Gareth R. Williams,**[3] **Christopher J. Branford-White,**[3] **Huali Nie,**[2] **Limin Zhu**[2]

[1]Key Laboratory of Science and Technology of Eco-Textiles, Donghua University, Ministry of Education, China
[2]College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai 201620, China
[3]UCL School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX, UK
Correspondence to: L. Zhu (E-mail: lzhu@dhu.edu.cn)

ABSTRACT: A facile and efficient protocol for the preparation of nanofibers incorporating polymeric ketoprofen prodrugs and polyvinylpyrrolidone was developed. Polymeric ketoprofen prodrugs were constructed by a two-step chemo-enzymatic synthetic route, and nanofibers prepared by electrospinning from dimethylformamide/ethanol (1 : 1, v/v) solutions. The morphological characteristics of the fibers were influenced by the concentration of active agent in the spinning solution; average diameters varied from 196 to 370 nm. *In vitro* release studies indicated that the ketoprofen release rate from the electrospun fibers was significantly higher than that from the pure polymeric prodrugs. Cumulative drug release from the electrospun fibers reached 40–70% after 3 h and 75–100% after 12 h, while the pure polymeric prodrug released only 7–9% of the active agent over 12 h. Functional nanofibers incorporating polymeric prodrugs therefore comprise potentially effective drug delivery systems for sustained release. © 2013 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 130: 1570–1577, 2013

INTRODUCTION

In recent years, polymer electrospinning has emerged as a powerful technique for the fabrication of nanofibrous materials.[1] Electrospun fibers have properties that make them attractive materials for a range of applications, including high specific surface areas (10–1000 $m^2 g^{-1}$),[2] high aspect ratios, high porosities (up to 80%), and controllable diameters (from nanometers to microns).[3] Control of fiber composition can be achieved through the blending, encapsulation, and immobilization of biological and other active components. Therefore, electrospun nanofibers show great promise in biomedicine, tissue engineering, water and air purification, *inter alia*.[4–8]

Remarkable progress has been made in the development of drug delivery systems in recent years, with the aim of maximizing therapeutic effects.[9–12] Since Kenawy et al. first examined drug release from electrospun fibrous mats,[13] drug delivery systems based on nanofibers have attracted increasing interest in the pharmaceutical field owing to the facile manipulation of chemical, physical, biological, and surface properties of the fibers.

Electrospun nanofibers can be used as carriers for various drugs and other biocompatible or bioactive molecules, and the active pharmaceutical agent (API) release profile can be controlled by modulation of the fiber scaffold structure and morphology, polymer composition, loading dosage, and the manner of API incorporation.[14] Consequently, electrospun nanofibers can offer site-specific delivery of drugs *in vivo*, and may be applicable in wound healing or implants in surgery.

A range of electrospinning techniques (e.g., conventional single-fluid, coaxial, or emulsion) have evolved, offering a number of different API-loading methods. Most research is focused on low-molecular-weight drugs[15–18] aiming to overcome challenges with short half-lives in the bloodstream, renal clearance, and initial burst release.[19] Nevertheless, the development of new composite nanofiber systems applicable to a wider range of drugs remains a challenging task.

Polymer-drug conjugates, in which drug moieties are covalently linked to a polymer chain through cleavable linkers,[20–22] offer numerous advantages over conventional low-molecular-weight drugs. They can deliver prolonged or sustained drug release,
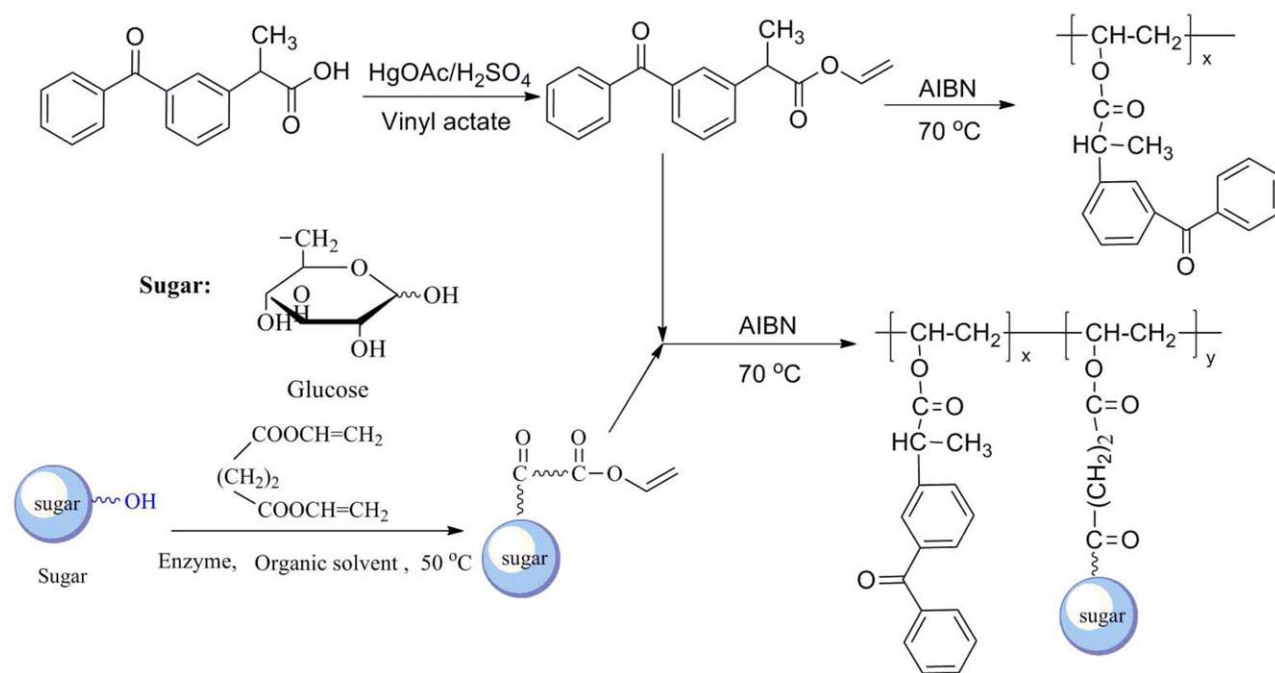
Scheme 1. The preparation of polymeric prodrugs with ketoprofen pendants. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

altered biodistribution, and reduced toxicity. Polymer-drug conjugates can also improve biocompatibility.[23,24] However, the drug release rate from polymer-drug conjugates is often slow, making it challenging to reach and maintain a therapeutic concentration in the plasma.[25–28] This effect is especially marked for homopolymeric prodrugs having high API content.[29,30] The combination of polymer–drug conjugates with the electrospinning technique could permit the development of bespoke drug delivery systems with sustained release properties, suitable for various applications in pharmaceutical science.

In the investigation reported here, two kinds of polymer-ketoprofen conjugates were synthesized following methods reported previously.[30] Nanofibers incorporating these polymer–drug conjugates were prepared via electrospinning with the polymer polyvinylpyrrolidone, which has excellent biocompatibility and physical properties.[31,32] The fibers have been comprehensively characterized by

FT-IR spectroscopy, scanning electron microscopy (SEM) and X-ray diffraction (XRD). The release profiles of ketoprofen from the nanofiber systems were investigated and compared. This represents the first report of a composite nanofiber-based drug delivery system containing a polymer–drug conjugate. The findings from this study are expected to contribute to the rational design of drug delivery systems for various biomedical applications.

EXPERIMENTAL

Materials

Ketoprofen (2-(3-benzoylphenyl) propionic acid) was purchased from the Hubel Biocause Pharmaceutical Company (Hubel, P.R. China). Polyvinylpyrrolidone (PVP) K60 ($M_w = 58,000$ Da) was obtained from Shanghai Yunhong Pharmaceutical Aids and Technology (Shanghai, P.R. China). All other chemicals used in this work were of analytical grade and were dried over 4-Å molecular sieves for 24 h prior to use.

Table I. The Compositions of the Polymer Solutions used for Electrospinning, with Diameters of the Resultant Fibers

| | Composition of spinning solution (% w/v) | | | | | | | | |
Fiber	a	b	c	d	e	f	g	m	n
PVP K60	10	12	12	12	10	10	10	8	10
Ketoprofen[a]	5	5	7	9	–	–	–	–	–
Poly-KVE[b]	–	–	–	–	5	7	9	15	–
Poly(KVE-co-VSUG)[c]	–	–	–	–	–	–	–	–	5
Fiber diameter (nm)	203 ± 17	189 ± 12	278 ± 28	259 ± 25	289 ± 33	265 ± 23	196 ± 15	370 ± 52	222 ± 37

[a] Particle diameter (μm) = 100–120.

[b] $M_n = 2.964 \times 10^4$, $M_w/M_n = 1.724$, Drug loading* (w/w %) = 41.1%, particle diameter (μm) = 3.58.

[c] $M_n = 1.709 \times 10^4$, $M_w/M_n = 1.341$, Drug loading* (w/w %) = 90.7%, particle diameter (μm) = 3.29.

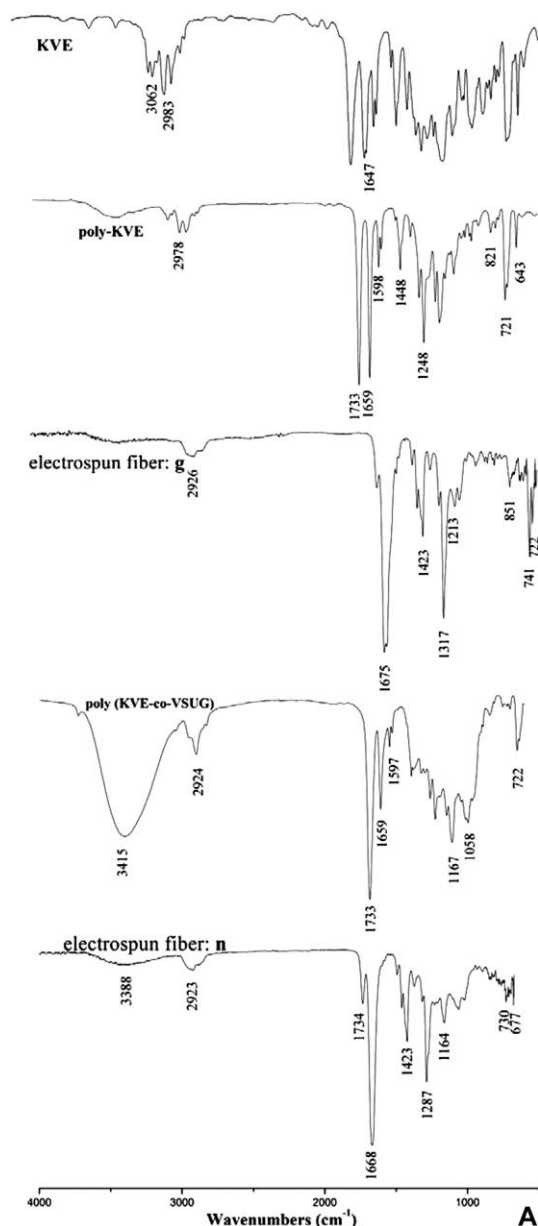Determined by the integration of ^{1}H NMR spectra.

Figure 1. (A) IR spectra of KVE, poly-KVE, poly(KVE-*co*-VSUG), and electrospun fibers g (10% PVP/9% poly-KVE) and n (10% PVP/5% poly(KVE-*co*-VSUG)); (B, C) NMR spectra of poly(KVE-*co*-VSUG). Parts B and C are reproduced with permission from Ref. 28. Copyright 2011 Wiley Periodicals Ltd.

Synthesis of Monomers

Polymerizable ketoprofen vinyl ester (KVE) and a glucose derivative (VSUG) were synthesized and purified as described in previous work.[33–35] The experimental approach is outlined in Scheme 1.

Preparation of Homopolymeric Prodrug (poly-KVE).

KVE was placed in a 10-mL sealed polymerization tube and 2% AIBN (w/w) was added as an initiator. Polymerization was conducted under an atmosphere of N_2 at 70°C for 4 h, and the reaction then halted by adding acetone to precipitate the polymeric prodrug. ^{1}H NMR (CDCl$_3$): δ (ppm): 7.35–7.81 (m, 9H, Ar-H), 4.74 (s, 1H, ($-$CHCH$_2-$)$_n$), 3.60 (s, 1H, $-$C$_6$H$_4$CH), 1.66–1.26 (m, 5H, ($-$CHCH$_2-$)$_n$, $-$CH$_3$). ^{13}C NMR (CDCl$_3$): δ (ppm): 196.1, 173.1

(C$=$O), 137.8, 137.5, 132.5, 132.4, 131.6, 130.0, 129.3, 129.2, 129.1, 128.7, 128.5, 128.3 (Ar, ketoprofen), 68.8 (C-3, ketoprofen), 68.6 (C-2, ketoprofen), 45.2 ($-$CHCH$_3$, ketoprofen), 29.5 (($-$CHCH$_2-$)$_n$), 18.4 ($-$CHCH$_3$, ketoprofen). IR (KBr): ν (cm^{-1}): 1733 (O$-$C$=$O), 1659, 1596, 1580, 821, 721, 643 (Ar).

Copolymerization of Polymeric Ketoprofen-Glucose Conjugate (Poly(KVE-co-VSUG)).

A mixture containing KVE and VSUG (1 : 1 molar ratio), AIBN (2 %, w/w), and *N,N*-dimethylformamide (DMF; 1 µL mg^{-1}) were combined in a 10-mL sealed polymerization tube, and stirred at 70°C under N_2 for 6 h. The resulting product was repeatedly precipitated in methanol and then dried under reduced pressure. IR (KBr): ν (cm^{-1}): 3415, 1167, 1058 (OH), 1733 (O$-$C$=$O), 1659, 1597, 1448, 821, 722, 643 (Ar). ^{1}H NMR (DMSO-d$_6$): δ (ppm): 7.48–7.62 (d, 9H, Ar-H), 6.7 (br s, 0.58 H, β 1-OH of D-glucose), 6.33 (br s, 0.42H, α 1-OH of D-glucose), 5.06–4.42 (br m, other OH of D-glucose), 4.31 (m, 1.5 H, H-6 (1H) and β H-1 (0.5 H) of D-glucose), 3.99 (m, 1 H, H-6′ of D-glucose), 3.80 (m, 0.5 H, α H-5 of D-glucose), 3.45–3.34, 3.15, 3.05 (br m, other α or β H of D-glucose), 2.93 (m, 0.5 H, β H-2 of D-glucose), 2.67–2.51 (m, 4 H, $-$CH$_2$$-CH_2$$-$ of butanedioyl part), 1.64–1.35 ($-$CHCH$_3$, ketoprofen, $-$CH$_2-$). ^{13}C NMR (DMSO-d$_6$): δ (ppm): 198.2, 174.6 (C$=$O), 139.9, 139.7, 135.4, 132.3, 131.2 (Ar, ketoprofen), 99.7 (C1 of β-D-glucose), 95.1 (C1 of α-D-glucose), 79.2 (C3 of β-D-glucose), 77.4 (C2 of β-D-glucose), 76.2 (C5 of β-D-glucose), 75.7 (C3 of α-D-glucose), 74.9 (C2 of α-D-glucose), 73.4 (C4 of α-D-glucose), 72.9 (C4 of β-D-glucose), 71.8 (C5 of α-D-glucose), 67.2 (C6 α, β-D-glucose), 47.2 ($-$CHCH$_3$, ketoprofen), 42.9, 42.7, 42.5, 42.3, 41.9, 41.7 ($-$CH$_2-$), 31.2 (($-$CHCH$_2-$)$_n$), 21.2 ($-$CHCH$_3$, ketoprofen).

Preparation of Spinning Solutions

Ketoprofen, poly-KVE, poly(KVE-*co*-VSUG) and PVP K60 were dissolved in DMF/ethanol (1 : 1 v/v) at ambient conditions (temperature 24–25°C and relative humidity ~65%). Solutions of various concentrations were prepared and are detailed in Table I. The solutions were degassed with a SK5200H ultrasonicator (350 W, Shanghai Jinghong Instrument, Shanghai, P.R. China) for 30 min prior to spinning.

Electrospinning

Spinning solutions were placed in a syringe (10 mL) fitted with a metal needle (0.5 mm diameter). A high-voltage power supply (ZGF60KV/2 mA, Shanghai Sute, Shanghai, P.R. China) was used to provide a voltage of 10 kV. The positive electrode of the high-voltage power supply was connected to the needle tip. The earthed electrode was connected to a metal collector wrapped with aluminum foil. Electrospinning was carried out under ambient conditions, and fibers collected 15 cm from the syringe tip. The feed rate of solutions was maintained at 0.8 mL h^{-1} by means of a single syringe pump (KDS100, Cole-Parmer, IL, USA). After electrospinning, fibers were dried at 35°C under vacuum (320 Pa) in a DZF-6050 Electric Vacuum Drying Oven (Shanghai Laboratory Instrument Work, Shanghai, P.R. China) to remove residual organic solvents and water.

Characterization

The structures of the polymer products were confirmed by FT-IR spectroscopy and nuclear magnetic resonance (NMR, Bruker-DQX 500 NMR instrument, Brüker Physik AG,
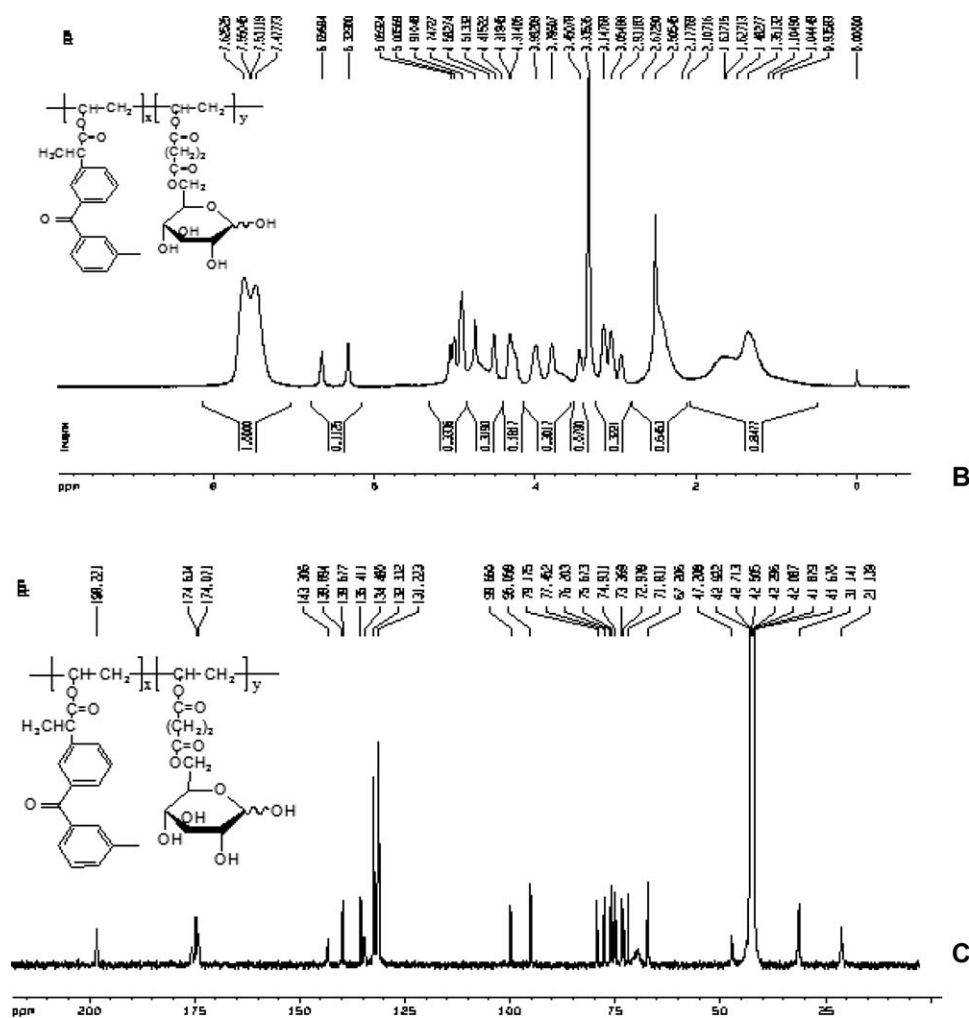
Figure 1. (Continued)

Karlsruhe Forchheim, Germany). The molecular weights of the polymers were confirmed by BI-MwA GPC (gel permeation chromatography, Waters, LS: Brookhaven, USA: experimental conditions, mobile phase: DMF; run time: 50 min; column temperature: 50°C). Scanning electron microscopy (SEM, JSM-5600LV instrument, JOEL, Tokyo, Japan) was used to investigate the macroscopic morphology and surface texture of the electrospun fibers. FT-IR spectra were obtained using a Nicolet-Nexus 670 FT-IR spectrometer. X-ray diffraction (XRD) patterns were obtained on a D/Max-BR diffractometer (Rigaku, Tokyo, Japan) with Cu Kα radiation in the 2θ range 5°–60° at 40 mV and 30 mA.

Release Study
Preparation of Phosphate Buffer Solution. A phosphate buffer solution (pH 7.4) was prepared by dissolving dibasic sodium phosphate (Na_2HPO_4; 21.70 g) and monobasic potassium phosphate (KH_2PO_4; 2.60 g) in 1 L deionized water. The pH was subsequently adjusted to 7.4 using 0.1 N sodium hydroxide and 0.1 N hydrochloric acid solutions.

Drug Release. The *in vitro* release of ketoprofen from its polymer conjugates and nanofibers was investigated at pH 7.4 and 37°C using a drug release instrument (RCZ-8A dissolution apparatus, Tianjin University Radio Factory, Tianjin, P.R. China). About 10 mg

of the ketoprofen polymer conjugates or nanofibers were added to 1 mL of the release buffer solution and subsequently placed into a dialysis membrane (MWCO = 3500). The dialysis membrane was then transferred into a 10-mL bottle with a further 5 mL of buffer solution and the medium was stirred at a rate of 100 rpm at 37°C. At appropriate time intervals, the entire release medium was withdrawn and replaced with an equal amount of fresh medium. The aliquots were analyzed by HPLC (Waters 510 with a reverse-phase Shim-Pack VP-ODS column (150×4.6 mm^2), mobile phase: methanol/water, 80/20 v/v; wavelength: 254 nm; flow velocity: 1 mL min^{-1}). The amount of ketoprofen released from the nanofibers was calculated using a predetermined calibration curve. Experiments were conducted in triplicate, and are reported as mean ± S.D.

RESULTS AND DISCUSSION

Polymer-drug conjugates were first prepared following methods developed in our previous research,[28] which are illustrated in Scheme 1. Subsequently, these conjugates were incorporated into electrospun fibers. Each of these was assessed as a possible drug delivery device.

Characterization of Polymeric Prodrugs and Electrospun Fibers
The structures of the polymeric prodrug products were confirmed by FT-IR and NMR. Taking poly(KVE-*co*-VSUG) as an
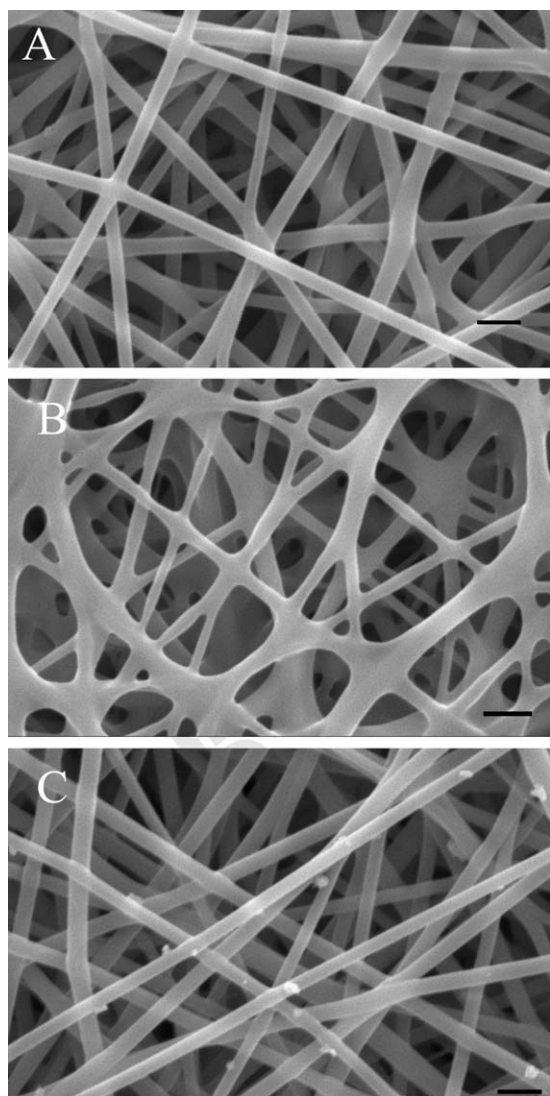
Figure 2. SEM micrographs of electrospun fibers d, m, and n. (A) fiber d: PVP 12%, ketoprofen 9% (w/v); (B) fiber m: PVP 8%, poly-KVE 15% (w/v); (C) fiber n: PVP 10%, poly(KVE-co-VSUG) 5% (w/v).

example, the IR spectrum showed that the vinyl group absorption in the KVE monomer (1647 cm^{-1}) disappeared in the polymer [Figure 1(A)]. Characteristic absorptions assigned to D-glucose moieties (3415, 1167, 1058 cm^{-1}) and aromatic rings (1659, 1597, 1448, 821, 722, 643 cm^{-1}) were evident in the spectrum of the polymer.

NMR data also revealed the disappearance of vinyl group from the monomer upon polymerization (^{1}H NMR: δ 7.28, 4.86, 3.88; ^{13}C NMR: δ 143.6, 100.4). The presence of ketoprofen (^{1}H NMR: δ 7.62, 7.48; ^{13}C NMR: δ 143.3, 139.9, 139.7, 135.4, 134.5, 132.3, 131.2, 47.2, 42.9), glucose groups (^{1}H NMR: δ5.06–3.45; ^{13}C NMR: δ 99.7, 95.1, 79.2, 77.5, 76.2, 75.7, 74.9, 73.4, 72.9, 71.8, 67.2) and the poly(vinyl alcohol) main chain (^{1}H NMR: δ2.18–1.63; ^{13}C NMR: δ 31.2) are clearly evident in the polymer: see Figure 1(B,C). Thus, the results from IR and NMR spectra clearly demonstrate that a conjugate product was formed. It was estimated from NMR spectra that the ratio of

drug vinyl ester to VSUG in the copolymer was 0.72 : 1, and the drug loading was 41.07 wt % (Table I).

FT-IR spectroscopy was also used to characterize the fibers, and investigate the interactions between PVP and ketoprofen or polymeric ketoprofen prodrugs. Typical results for poly-KVE and poly(KVE-co-VSUG) nanofibers (**g** and **n,** respectively) are given in Figure 1(A). The key features of the IR spectra of fibers **g** (10% PVP/9% poly-KVE) and **n** (10% PVP/5% poly(KVE-co-VSUG)) were largely identical to the main absorption bands of poly-KVE and poly(KVE-co-VSUG), respectively. This indicated that there was no difference between the internal structures and conformation of the prodrugs at the molecular level. The multiplet observed around 2978 cm^{-1} in the spectrum of poly-KVE [Figure 1(A)] and attributed to C—H stretching vibrations was completely covered by bond stretches from PVP and is not visible in the poly-KVE fibers (**g**). The carbonyl stretch modes of the carboxylic acid appearing at 1733 cm^{-1} for poly-KVE and 1662 cm^{-1} for PVP were merged together for fiber **g**. Similarly, the band at 3415 cm^{-1} attributed to the O—H of poly(KVE-co-VSUG) decreased in intensity and almost disappeared from the spectra of its fiber (fiber **n**). Interactions in the medicated fibers between ketoprofen and PVP will comprise hydrogen bonds formed between the C=O of PVP and the —OH of ketoprofen, reflecting the good compatibility of ketoprofen and PVP.[36]

SEM Characterization of Electrospun Fibers

Figure 2 shows SEM images of selected electrospun fibrous mats. These possess the common features of being bead-free, randomly arrayed, and appear highly porous. Average diameters of 259 ± 25, 370 ± 52 and 222 ± 37 nm were obtained for fibers **d** (12% PVP/9% ketoprofen), **m** (8% PVP/15% poly-KVE) and **n** (10% PVP/5% poly(KVE-co-VSUG)), respectively (see Table I). In Figure 2(A,B), the fiber surfaces are smooth, and no drug crystals could be detected, while in Figure 2(C) granules can be observed at the nanofiber surfaces. This indicated that ketoprofen or its homopolymer prodrug were fully incorporated into the electrospun fibers **d** and **m**, but the poly(KVE-co-VSUG) copolymer is sequestered onto the fiber surface to an extent in fiber **n**.

The fibers produced at all polymer concentrations show porous structures comprised of randomly oriented non-woven fibers of variable submicron to micron diameters. Figure 3 illustrates a representative sample of the morphologies obtained using different concentrations of PVP K60 and ketoprofen or poly-KVE. The images clearly show that the combination of low polymer and drug concentrations leads to the formation of beaded fibers. At concentrations of 10% (w/v) PVP and 5% ketoprofen [fiber **a**, Figure 3(A)] or 10% PVP with 5% (w/v) poly-KVE [fiber **e**, Figure 3(C)], nanofibers with "bead on a string" morphology are observed. Increasing the polymer concentration to 12% (w/v) PVP K60 with 5 % ketoprofen [Figure 3(B)] leads to the formation of fibers with consistent structures and minimum beading. Increasing the concentration of poly-KVE to 7 or 9% with 10% PVP [fibers **e** and **f**; Figure 3(D,E)] has the same effect. Thus, the electrospinning of higher concentration
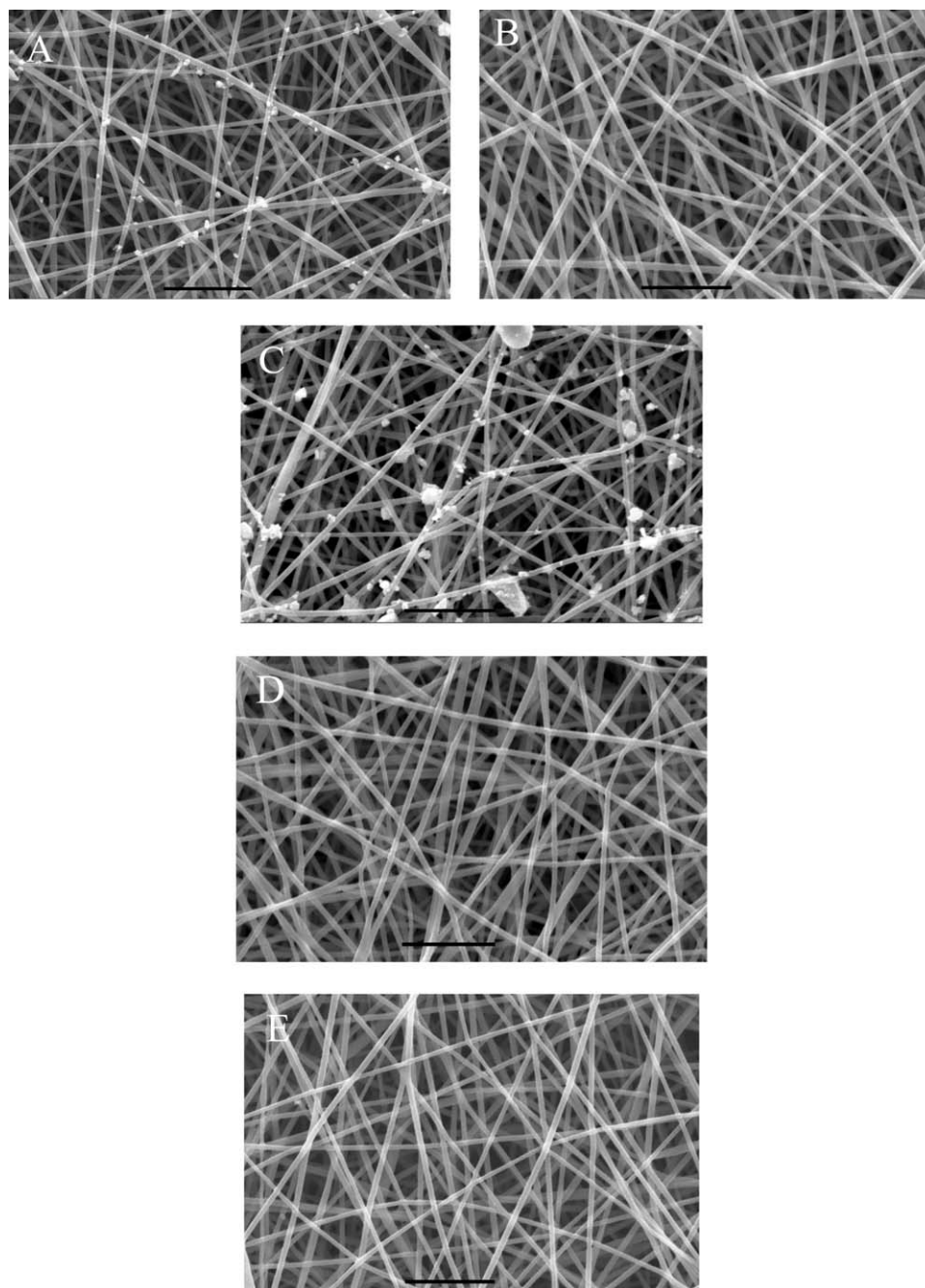
Figure 3. SEM micrographs of electrospun fibers obtained using solutions a, b, e, f and g. (A) fiber a: 10% PVP, 5% ketoprofen (w/v); (B) fiber b: 12% PVP, 5% ketoprofen (w/v); (C) fiber e: 10% PVP, 5% poly-KVE (w/v); (D) fiber f: 10% PVP, 7% poly-KVE (w/v); (E) fiber g: 10 % PVP, 9% (w/v) poly-KVE (w/v).

solutions leads to the formation of fibers with smooth surface morphologies and without the presence of any type of beaded structure. It was observed that the fiber diameter decreases with increasing concentration of PVP (**a**, **b**) or poly-KVE (**e**, **f**, **g**): see Table I for details.

X-ray Diffraction

Selected XRD patterns are displayed in Figure 4. The presence of numerous distinct reflections in the XRD pattern of ketoprofen [Figure 4(A)] indicates that the drug is present as a crystalline material with characteristic diffraction peaks appearing at $2\theta = 6.36°$, $16.2°$, $18.34°$, and $23.88°$. In contrast, the data in Figure 4(B) demonstrate that poly(KVE-*co*-VSUG) is an amorphous material, exhibiting only a broad hump centered at around $2\theta = 20°$. The pattern of pure PVP fibers [Figure 4(D)] is characterized by the complete absence of any reflections. For fiber **n**, the broad hump observed for poly(KVE-*co*-VSUG) cannot be seen in the XRD pattern [Figure 4(C)] but there are no reflections visible, indicating that poly(KVE-*co*-VSUG) remains present in an amorphous state.
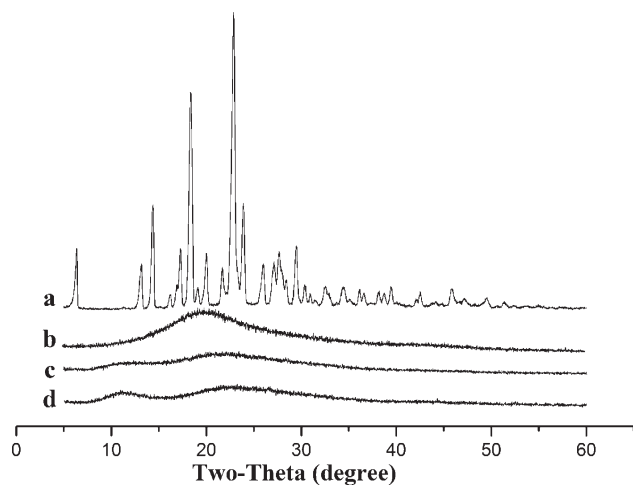
Figure 4. Selected XRD patterns: a: ketoprofen; b: poly(KVE-*co*-VSUG); c: fiber n (PVP 10%, poly(KVE-*co*-VSUG) 5%); d: fiber a (10% PVP, 5% ketoprofen).
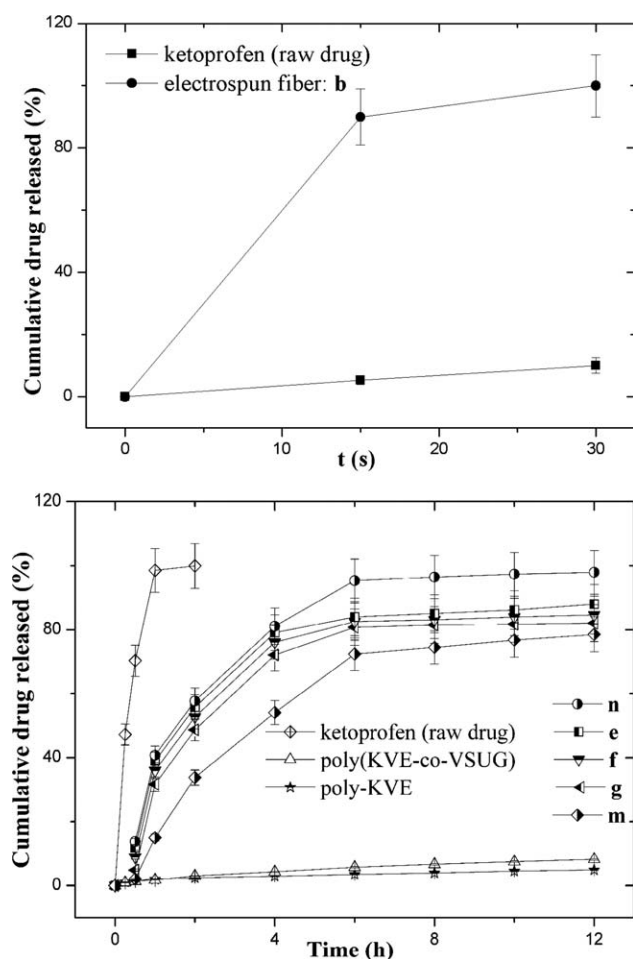

Figure 5. Cumulative drug release (%) from (A) pure ketoprofen and fiber b (12% PVP, 5% ketoprofen); (B) pure ketoprofen, polymer prodrugs and electrospun prodrug fibers. All data were recorded at pH 7.4, and 37°C.

In Vitro Drug Release

The release of ketoprofen from its conjugates and electrospun fibers was investigated at pH 7.4 and 37°C. HPLC was used to quantitatively analyze the extent of drug release using a predetermined calibration curve. In all cases, the HPLC profiles and NMR spectra of the release solutions confirmed that it was monomeric ketoprofen which was freed from the polymer matrices.

From Figure 5(A), it can be seen that ketoprofen was released extremely rapidly from the PVP/ketoprofen fiber **b**, with 89.9% being released within 15 s, and complete release after 30 s. In contrast, over the same time interval only about 10% of the ketoprofen was released from the raw drug particles. This confirmed that the incorporation of ketoprofen into fibers increased the rate of drug release, presumably because of their large surface areas and the easy dissolution of PVP. However, the fibers would not deliver an effective therapeutic effect because they do not provide sustained release of the drug.

Poly-KVE and its polymeric ketoprofen-glucose conjugate (poly (KVE-*co*-VSUG)) were also investigated for drug release [see Figure 5(B)]. For pure ketoprofen, the drug is freed into solution fairly quickly, with almost 100% release detected after 2 h. Over the same time interval only 3% of ketoprofen was released from poly(KVE-*co*-VSUG), and a similar amount from poly-KVE. Drug release from poly-KVE and poly(KVE-*co*-VSUG) reached 25 and 41% respectively after 228 h. This confirmed that polymeric keto-profen–saccharide conjugates prolonged drug release effectively. The data implied that the amount of drug release from poly(-KVE-*co*-VSUG) was higher than from poly-KVE, suggesting that the glucose branch in poly(KVE-*co*-VSUG) influenced the release capabilities of the prodrug. This could be owing to the good water-solubility of sugar.

However, the release of drug from these conjugates was found to be too slow for therapeutic purposes, especially from poly-KVE. Incorporation of the prodrugs into nanofibers was found, in general, to lead to more rapid release rates [Figure 5(B)]. It can be seen from Figure 5(B) that electrospun fiber **n** (10% PVP/5% poly(KVE-*co*-VSUG)) had the highest release rate, reaching almost 100% after 12 h. The analogous fiber containing poly-KVE (**e**; 10% PVP/5% poly-KVE) displayed slower release than fiber **n**, with the former releasing around 70% of the incorporated keto-profen after 3 h and around 80% after 12 h.

Comparing the ketoprofen release profiles from fibers **e** (10% PVP/5% poly-KVE w/v), **f** (10% PVP/7% poly-KVE), **g** (10% PVP/9% poly-KVE) and **m** (8% PVP/15% poly-KVE), it can be found that the rate and extent of drug release generally decreases with increasing poly-KVE content. It is therefore possible to control the drug release rate by varying the concentration of poly-KVE in the solution used for electrospinning.

The cumulative ketoprofen release from the electrospun fibers was about 40–75% within the first 3 h, rising to about 75–100% after 12 h. The initial burst release could allow the necessary therapeutic drug concentration to be attained rapidly. An initial burst of drug followed by sustained release is normally regarded as being appropriate for therapeutic studies, compensating for metabolic losses.

Overall, release studies in buffer solution indicated that the use of electrospun fibers containing polymeric prodrugs can effectively prolong the release of the parent drug, and permit the drug release pattern to be manipulated to achieve clinical requirements.

Ketoprofen can be used for the treatment of a wide variety of conditions, including the treatment of migraine headaches, to provide analgesic action for sports injuries and in gynecological conditions *inter alia*.[37] There have also been suggestions that it may be useful in the prevention of colorectal and lung cancers, or for treatment of Parkinson's disease. Typical doses are of the order of 50–100 mg, with repeated applications every 6–8 h. Prolonged application of the drug over days, weeks, or months may be required, and hence sustained release formulations are of great interest. The maximum dose given is generally 300 mg per day; the most concentrated fiber mats contain around 27% ketoprofen by mass, and hence to deliver 300 mg ∼1.1 g of fiber mat would be required. This is not an unreasonable amount for a dosage form, which suggests that, with further optimization, the electrospun materials reported here could be eminently suitable for clinical application.

CONCLUSION

A family of novel drug delivery systems comprising electrospun nanofibers incorporating ketoprofen polymeric prodrugs and polyvinylpyrrolidone has been developed. The medicated fibers appeared smooth and uniform. The morphology of the fibers was influenced by the concentration of the pharmaceutical and polymer components in the spinning solutions. The drug release behavior of the systems varied with their composition and morphology. Generally, drug release from the electrospun prodrug fibers was rapid initially, and followed by a sustained release phase. These findings suggest that the controlled release of drugs from prodrug-containing electrospun PVP fibers could be potentially useful in drug delivery systems.

REFERENCES

1. Sundarrajan, S.; Venkatesan, A.; Ramakrishna, S. *Macromol. Rapid Commun.* **2009**, *30*, 1769.

2. Kalra, V.; Lee, J. H.; Park, J. H.; Marquez, M.; Joo, Y. L. *Small* **2009**, *5*, 2323.

3. Yoon, K.; Hsiao, B. S.; Chu, B. *J. Mater. Chem.* **2008**, *18*, 5326.

4. Meli, L.; Miao, J. J.; Dordick, J. S.; Linhardt, R. *J. Green Chem.* **2010**, *12*, 1883.

5. Xu, X.; Yang, L.; Xu, X.; Wang, X.; Chen, X.; Liang Q. *J. Control. Release* **2005**, *108*, 32.

6. Pitarresi, G.; Palumbo, F. S.; Fiorica, C. *Eur. Polym. J.* **2010**, *46*, 81.

7. Kenawy, E. R.; Bowlin, G. L.; Mansfield, K.; Layman, J.; Simpson, D. G.; Sanders, E. H.; Wnek, G. E. *J. Control. Release* **2002**, *81*, 57.

8. Huang, Z. M.; Zhang, Y. Z.; Kotaki, M.; Ramakrishna, S. *Compos. Sci. Technol.* **2003**, *63*, 2223.

9. Agarwal, S.; Wendorff, J. H.; Greiner, A. *Polymer* **2008**, *49*, 5603.

10. Goldberg, M.; Langer, R.; Jia X. *J. Biomater. Sci. Polym. Ed.* **2007**, *18*, 241.

11. Zong, X.; Kim, K.; Fang, D.; Ran, S.; Hsiao, B. S.; Chu, B. *Polymer* **2002**, *3*, 4403.

12. Sill, T. J.; von Recum, H. A. *Biomaterials* **2008**, *29*, 1989.

13. Kenawy, E. R.; Bowlin, G. L.; Mansfield, K.; Layman, J.; Simpson, D. G.; Sanders, E. H.; Wnek, G. E. *J. Control. Release* **2002**, *81*, 57.

14. Venugopal, J.; Low, S.; Choon, A. T.; Ramakrishna, S. *J. Biomed. Mater. Res. B* **2008**, *84b*, 34.

15. Nie, H.; Wang, C. H. *J. Control. Release* **2007**, *120*, 111.

16. Zhang, Y. Z.; Wang, X.; Feng, Y.; Li, J.; Lim, C. T.; Ramakrishna, S. *Biomacromolecules* **2006**, *7*, 1049.

17. Qi, H.; Hu, P.; Xu, J.; Wang, A. *Biomacromolecules* **2006**, *7*, 2327.

18. Quan, J.; Yu, Y.; Branford-White, C.; Williams, G. R.; Yu, D. G.; Nie, W.; Zhu, L. M. *Colloid Surf. B Biointerfaces* **2011**, *88*, 304.

19. Haag, R.; Kratz, F. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 1198.

20. Xu, D. Y.; Li, G. J.; Liao, Z. F.; He, X. H. *Polym. Bull.* **2009**, *62*, 183.

21. Davis, B. G.; Robinson, M. A. *Curr. Opin. Drug Discov. Dev.* **2002**, *5*, 279.

22. Li, X.; Lu, M.; Wu, Q.; Lv, D. S.; Lin, X. F. *J. Polym. Sci. Polym. Chem.* **2008**, *46*, 117.

23. Khandare, J.; Minko, T. *Prog. Polym. Sci.* **2006**, *31*, 359.

24. Chung, I.; Lee, C. K.; Ha, C. S.; Cho, W. J. *J. Polym. Sci. A Polym. Chem.* **2006**, *44*, 295.

25. Ricci, M.; Blasi, P.; Giovagnoli, S.; Rossi, C.; Macchiarulo, G.; Luca, G.; Basta, G.; Calafiore, R. J. *J. Control. Release* **2005**, *107*, 395.

26. Maestrelli, F.; Zerrouk, N.; Cirri, M.; Mennini, N.; Mura, P. *Eur. J. Pharm. Sci.* **2008**, *34*, 1.

27. Roda, A.; Sabatini, L.; Mirasoli, M.; Baraldini, M.; Roda, E. *Int. J. Pharm.* **2002**, *241*, 165.

28. Wu, C. Y.; Xie, J. G.; Branford-White, C.; Quan, J.; Zhu, L. M. *J. Appl. Polym. Sci.* **2011**, *121*, 1654.

29. Wu, C. Y.; Quan, J.; Xie, J. G.; Branford-White, C.; Zhu, L. M. *Polym. Bull.* **2011**, *67*, 593.

30. Karavas, E.; Georgarakis, M.; Docoslis, A. *Int. J. Pharm.* **2007**, *340*, 76.

31. Van den Mooter, G.; Augustijns, P.; Blaton, N.; Kinget, R. *Int. J. Pharm.* **1998**, *164*, 67.

32. Leuner, C.; Dressman, J. *Eur. J. Pharm. Biopharm.* **2000**, *50*, 47.

33. Cai, X. Q.; Wan, N.; Lin, X. F. *Polymer* **2006**, *19*, 6491.

34. Quan, J.; Wu, Q.; Lin, X. F. *Polymer* **2007**, *48*, 2595.

35. Quan, J.; Wu, Q.; Zhu, L. M.; Lin, X. F. *Polymer* **2008**, *49*, 3444.

36. Yu, D. G.; Zhang, X. F.; Shen, X. X.; Zhu, L. M. *Polym. Int.* **2009**, *58*, 1010.

37. Rencber, S.; Karavana, S. Y.; Ozyazici, M. *FADAB J. Pharm. Sci.* **2009**, *34*, 203.