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pH-responsive nanofibers with controlled drug release properties

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Smart polymers and nanofibers are potentially intriguing materials for controlled release of bioactive agents. This work describes a new class of pH responsive nanofibers for drug delivery systems with controlled release properties. Initially, poly(4-vinylbenzoic acid-*co*-(*ar*-vinylbenzyl)trimethylammonium chloride) [poly(VBA-*co*-VBTAC)] was synthesized *via* reversible addition–fragmentation chain transfer (RAFT) polymerization. Then, ciprofloxacin was chosen as the model drug for the release study and encapsulated into pH-responsive polymeric carriers of poly(VBA-*co*-VBTAC) nanofibers *via* electrospinning. The morphology of the electrospun nanofibers was examined by scanning electron microscopy (SEM). The structural characteristics of the pH responsive nanofibers were investigated by Fourier transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD). The release measurements of ciprofloxacin from pH responsive nanofibers were also performed by high-performance liquid chromatography (HPLC) analysis. To show the pH sensitivity of these nanofibers, the release profile of ciprofloxacin was examined under acidic, neutral and basic conditions. The results indicate that pH responsive nanofibers can serve as effective drug carriers since the release of ciprofloxacin could be controlled by changing the pH of the environment, and therefore these drug loaded pH-responsive nanofibers might have potential applications in the biomedical field.

Introduction

Controlled drug release systems have gained much attention in the last few decades and become an important topic in medicine, due to various advantages such as improved therapeutic efficacy and reduced toxicity by delivering the drug at controlled rates.[1–3] Several synthetic and/or natural polymers have been reported for controlled release studies.[4–6] In particular "smart" or "stimuli-responsive" polymers demonstrated their potential as effective carriers for controlled release.[7,8] The characteristic feature that makes them smart is their ability to respond to the very slight changes in the environment such as temperature, pH, electric field, light or magnetic field.[8–10] In addition, the morphological form of the carrier matrix becomes a key factor affecting the release behavior. For instance, polymer based drug carriers can be broadly classified into one of the following categories: nanoparticles, nanogels, micelles, hydrogels and electrospun nanofibers, each with certain advantages and disadvantages.[11]

Electrospinning has become the most attractive nanofiber production technique in the past decade due to its cost-effectiveness and versatility. This technique facilitates the production of ultrafine fibers from a variety of materials such as polymers (synthetic and/or natural), polymer blends, sol–gels, composites, *etc.*[12–14] In the electrospinning process, a continuous filament is electrospun from polymer solutions or polymer melts under a very high electrical field, which resulted in ultrafine fibers ranging from tens of nanometres to a few microns in diameter. Such nanofibrous structures have been proposed for a number of applications due to their very high surface-to-volume ratio with highly porous structures.[12,13] The morphology of electrospun nanofibers can be controlled by optimizing the factors such as electrospinning process parameters, the polymer solution, and environmental conditions.[12,13] Further functionalizations of electrospun nanofibers by physical/chemical post-treatments or incorporating active agents during the electrospinning process are also quite feasible for obtaining multifunctional nanofibrous materials. Due to the exclusive properties of electrospun nanofibers and their nanofibrous webs, these are very promising candidates for membranes/filters, biotechnology, textiles, sensors, energy, electronics, and the environment.[12–21] Especially, electrospun nanofibers can be ideal materials for drug delivery systems[20–23] since encapsulation of drugs inside the nanofiber matrix can be readily achieved by electrospinning where the target drug is dissolved in the desired polymer solution. Numerous studies

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have described the preparation of electrospun nanofibers containing pharmacologically active compounds and investigated the release characteristics of drugs.[22–29] Yet, the studies dealing with the combination of pH responsive polymers and nanofibers for the drug delivery systems are very limited in the literature.[30]

In this study, we developed pH-responsive poly(4-vinylbenzoic acid-*co*-(*ar*-vinylbenzyl)trimethylammonium chloride) [poly(VBA-*co*-VBTAC)] nanofibers for controlled drug release study. Poly(VBA-*co*-VBTAC) was synthesized *via* reversible addition–fragmentation chain transfer (RAFT) polymerization and pH responsive nanofibers encapsulating ciprofloxacin were produced by electrospinning. The morphological, structural and thermal characterization of the pH responsive nanofibers were performed by using scanning electron microscopy (SEM), Fourier transform infrared (FTIR) and X-ray diffraction (XRD). In order to investigate the pH responsive behavior, the release profile of ciprofloxacin from nanofibers was examined under acidic, neutral and basic conditions.

Materials and methods

Materials

(*ar*-Vinylbenzyl)trimethylammonium chloride (VBTAC, 99%, Aldrich), 4,4′-azobis(4-cyanopentanoic acid) (ACPA, ≥98%, Aldrich), 4-cyano-4-(phenylcarbonothioylthio)pentanoic acid (CPAD, 97%, Aldrich), ciprofloxacin (≥98%, Sigma-Aldrich), potassium phosphate monobasic dihydrate (≥98.0%, Sigma-Aldrich), sodium phosphate monobasic dihydrate (Sigma-Aldrich), sodium chloride (99.0–100.5%, Sigma-Aldrich), sodium acetate trihydrate (≥98.0%, Sigma-Aldrich), tris(hydroxymethyl)aminomethane (≥98.8%, Sigma-Aldrich), *N*,*N*-dimethylformamide (DMF, 99.8%, Sigma-Aldrich), acetone (≥99.8%, Sigma-Aldrich) and acetic acid (≥99.7%, Sigma-Aldrich) were purchased commercially. ACPA was recrystallized from methanol. 4-Vinylbenzoic acid (VBA) was prepared by a standard method[31] from α-bromo-*p*-toluic acid that was synthesized according to a previously published protocol.[32] Water was used from a Millipore Milli-Q ultrapure water system.

RAFT-mediated polymerization procedure

RAFT-mediated polymerization of VBA (30.0 mmol) and VBTAC (30.0 mmol) was performed with a 30 mL buffer solution (tris-buffered saline, pH = 7.5), a free RAFT agent CPAD (0.3 mmol) and an initiator ACPA (0.06 mmol) at 0 °C in a glass reactor. The solution was diluted to a 100 mL volume with a buffer solution and degassed by purging with nitrogen for 20 min. The polymerization solution was heated slowly (approximately 30 min) from 0 to 70 °C. The polymerization reaction solution (Fig. 1a) was stirred vigorously at 70 °C under a nitrogen atmosphere. After polymerization reaction, poly(VBA-*co*-VBTAC), which was collected at the bottom of the glass reactor, was filtered and dried at room temperature under vacuum. The yield of poly(VBA-*co*-VBTAC) was determined gravimetrically. The molecular weight distribution of the polymer was measured by aqueous size exclusion chromatography (ASEC).

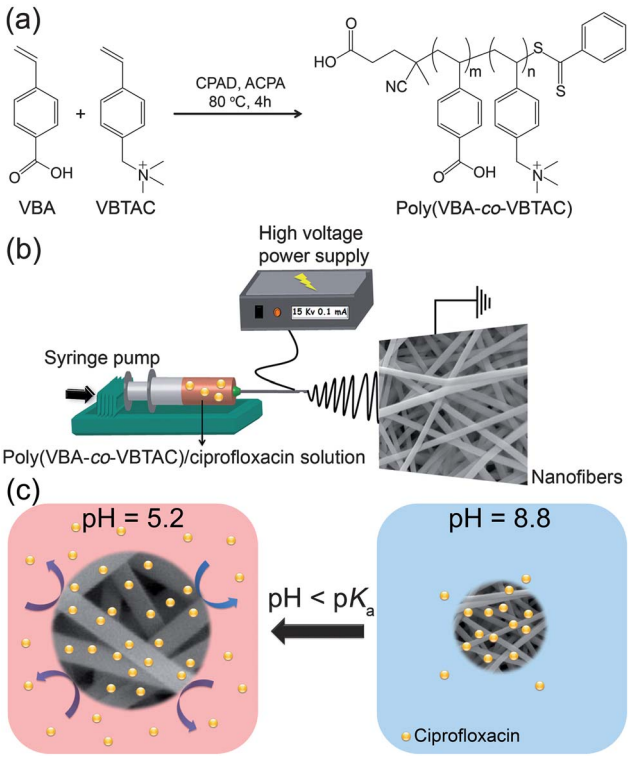

Fig. 1 (a) Synthesis of poly(VBA-*co*-VBTAC). Schematic representation of (b) electrospinning of ciprofloxacin encapsulated poly(VBA-*co*-VBTAC) nanofibers and (c) ciprofloxacin release from poly(VBA-*co*-VBTAC)/ciprofloxacin nanofibers.

Electrospinning

Firstly, a clear solution of poly(VBA-*co*-VBTAC) was prepared by dissolving in a DMF–acetic acid (7/3) binary solvent mixture at 15% (w/v) polymer concentration. Then ciprofloxacin was added into polymer solution at 5% (w/w, according to polymer). The ultimate ciprofloxacin included and not-included polymer solution was placed in a 3 mL syringe fitted with a metallic needle of 0.6 mm inner diameter. The syringe was fixed horizontally on the syringe pump (KDS 101, KD Scientific). The electrode of a high-voltage power supply (Matsusada Precision, AU Series) was clamped to the metal needle tip, and the cylindrical aluminum collector was grounded (Fig. 1b). The parameters of the electrospinning were adjusted as; feed rate of solutions = 1 mL h^{-1}, the applied voltage = 15 kV, and the tip-to-collector distance = 10 cm. Electrospun nanofibers were deposited on a grounded stationary cylindrical metal collector covered with a piece of aluminum foil. The electrospinning apparatus was enclosed in a Plexiglas box, and electrospinning was carried out at 25 °C at 25% relative humidity. The collected nanofibers were dried at room temperature under a fume hood overnight.

In vitro drug release studies

The release profile of ciprofloxacin from pH responsive nanofibers was investigated *via* high performance liquid chromatography (HPLC). A pH responsive nanofibrous mat

encapsulating ciprofloxacin was immersed in 30 mL of releasing media (acetate buffer solution, phosphate buffered saline and tris-buffered saline) at 37 °C for 720 minutes. 0.5 mL aliquot was withdrawn at predetermined time intervals up to 720 minutes and in order to keep the volume constant, the solution was replaced with the same volume of the fresh medium each time an aliquot was taken out (Fig. 1c). To determine the loading efficiency of ciprofloxacin in nanofibers, a known weight of the sample was taken from three different parts of the nanofibrous webs. These nanofibers and a known amount of ciprofloxacin were dissolved in dimethylformamide–acetic acid (7/3) solution. The solutions were stirred at room temperature, 0.5 mL of aliquot was withdrawn and the total amount of ciprofloxacin was determined by HPLC by three measurements. The HPLC results of nanofibers were compared with those of ciprofloxacin powder solution.

Measurements and characterization

The absolute molecular weights and dispersity of poly(VBA-*co*-VBTAC) were determined by ASEC at ambient temperature using Ultrahydrogel columns (120, 250, 500, and 1000 Å; Waters), a Wyatt Technology Optilab T-rEX RI detector ($\lambda = 690$ nm), a Wyatt Technology Dawn Heleos II multiangle laser light scattering detector ($\lambda = 658$ nm), and 1 wt% acetic acid–0.1 M Na_2SO_4(aq.) as the eluent with a flow rate of 1.0 mL min^{-1}. The d*n*/d*c* value of poly(VBA-*co*-VBTAC) (0.161 mL g^{-1}) in the above eluent was determined at 25 °C with a Wyatt Technology Optilab T-rEX RI detector ($\lambda = 690$ nm). The viscosity measurements of the electrospinning solutions were performed with a rheometer (Physica MCR 301, Anton Paar) equipped with a cone/plate accessory at a constant shear rate of 100 s^{-1} at 22 °C. The morphology and the diameter of the poly(VBA-*co*-VBTAC) and ciprofloxacin-loaded poly(VBA-*co*-VBTAC) [CIP-poly(VBA-*co*-VBTAC)] nanofibers were examined by using a scanning electron microscope (FE-SEM) (FEI, Quanta 200 FEG). Samples were sputtered with 5 nm Au/Pd (PECS-682) and around 100 fiber diameters were measured from the SEM images to calculate the average fiber diameter of each sample. The infrared spectra of the samples were obtained by using a Fourier transform infrared spectrometer (FTIR) (Bruker-VERTEX 70). The samples were mixed with potassium bromide (KBr) and pressed as pellets. The scans (64 scans) were recorded between 4000 and 400 cm^{-1} at a resolution of 4 cm^{-1}. The X-ray diffraction (XRD) (PANalytical X'Pert Powder Diffractometer) patterns of nanofibrous webs and ciprofloxacin powder were collected by using Cu Kα radiation in a range of $2\theta = 5$–30°. The released amount of ciprofloxacin from nanofibers was determined by high performance liquid chromatography (HPLC, Agilent, 1200 series) coupled with a VWD UV detector. The column was C18 (Agilent, particle size: 5 μm; column dimension: 150 mm × 4.6 mm) operating at 0.5 mL min^{-1}. The mobile phase for separation was 100% acetonitrile. The injection volume was 5 μL. The UV detector was set at 217 nm. The experiments were carried out in triplicate and the results were given as the average ± standard deviation.

Results and discussion

Preparation and characterization of pH responsive nanofibers

Poly(VBA-*co*-VBTAC) with 52% VBA content[33] was synthesized *via* RAFT polymerization. We prepared copolymers with relatively large molecular weights (approximately 32 000 g mol^{-1}, yield 86%, DI = 1.08) to obtain uniform nanofibers. The overall procedure to prepare pH responsive nanofibers is described in Fig. 1. The morphological properties of the prepared nanofibers were observed using SEM (Fig. 2). SEM imaging showed that the electrospun poly(VBA-*co*-VBTAC) nanofibers and ciprofloxacin encapsulated poly(VBA-*co*-VBTAC) (poly(VBA-*co*-VBTAC)/ciprofloxacin) nanofibers were bead-free and have a smooth morphology with an average fiber diameter (AFD) of 310 ± 65 and 445 ± 120 nm, respectively. The poly(VBA-*co*-VBTAC)/ciprofloxacin nanofibers have higher fiber diameter compared to poly(VBA-*co*-VBTAC) nanofibers because the viscosity of the solution increased from 0.38 Pa·s to 0.59 Pa·s when ciprofloxacin was added into the polymer solution (Table 1). So, the electrified jet is subjected to less stretching during the electrospinning process and thicker nanofibers were obtained.[12,34] Fig. 2 shows the optical images of pH responsive nanofibers before and after swelling in deionized water. The nanofibers were initially opaque and became translucent upon absorption of water.

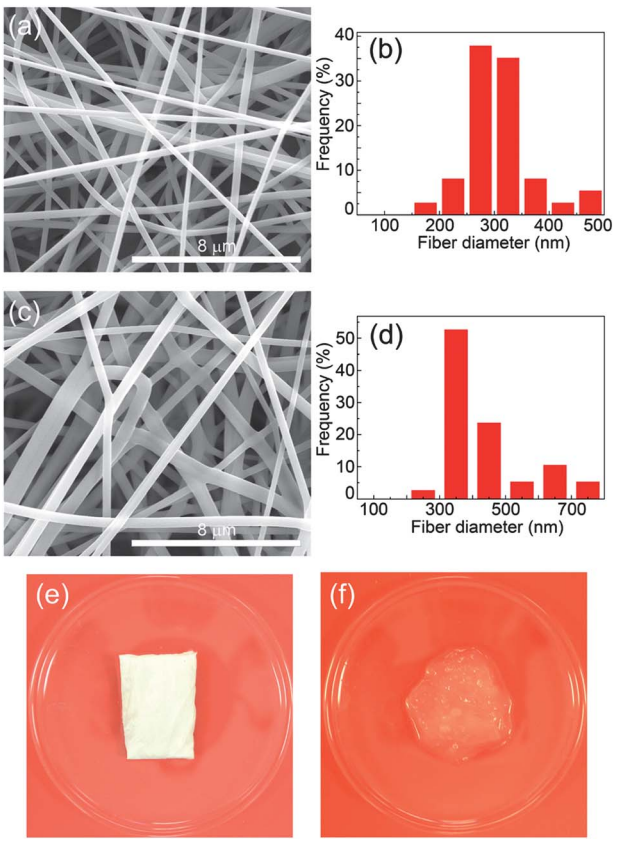

Fig. 2 The representative SEM images of (a) poly(VBA-*co*-VBTAC) nanofibers and (b) fiber diameter distribution; (c) poly(VBA-*co*-VBTAC)/ciprofloxacin nanofibers and (d) fiber diameter distribution; photographs of poly(VBA-*co*-VBTAC) nanofibrous mat (e) before and (f) after swelling in deionized water.

Table 1 The characteristics of poly(VBA-*co*-VBTAC) and poly(VBA-*co*-VBTAC)/ciprofloxacin solutions and the resulting electrospun fibers

Solutions	% Poly(VBA-*co*-VBTAC) (w/v)	% Ciprofloxacin (w/v)	Viscosity (Pa·s)	Fiber diameter (nm)	Fiber morphology
Poly(VBA-*co*-VBTAC)	15	—	0.38	310 ± 65	Bead-free nanofibers
Poly(VBA-*co*-VBTAC)/ ciprofloxacin	15	5	0.59	445 ± 120	Bead-free nanofibers

Fig. 3 shows the FTIR spectra of the ciprofloxacin and the electrospun nanofibers. The characteristic band of ciprofloxacin was observed at 1624 and 1272 cm^{-1} due to the vibration of phenyl framework conjugated to –COOH and the stretching vibration of the C–F bond, respectively. FTIR spectra of ciprofloxacin also showed an absorbance band at 3083 and 2918 cm^{-1} for the C–H stretching from the phenyl ring.[35,36] The peaks at 1670, 1480 and 1409 cm^{-1} were assigned to carbonyl (C═O), scissor $–CH_2–$ vibration and asymmetric $–CH_3$ deformation vibration of the poly(VBA-*co*-VBTAC) nanofibers, respectively. Through the FTIR spectra of poly(VBA-*co*-VBTAC)/ciprofloxacin nanofibers, it can be seen that absorption maxima of stretching vibration shifted toward lower wavenumbers compared to the pure ciprofloxacin and poly(VBA-*co*-VBTAC) nanofibers. All these results indicated that the model drug used in this work had strong hydrogen bonds and ionic bonds with the matrix of the poly(VBA-*co*-VBTAC) nanofibers. At the same time, there were no additional characteristic absorption bands for drug-loaded poly(VBA-*co*-VBTAC)/ciprofloxacin nanofibers elucidating that there was no noticeable chemical reaction between the drug and the nanofiber matrix. This is an important indication that ciprofloxacin would keep its activity in the poly(VBA-*co*-VBTAC)/ciprofloxacin nanofibrous matrix.

The X-ray diffraction (XRD) patterns of ciprofloxacin and the nanofibrous mats of poly(VBA-*co*-VBTAC) and poly(VBA-*co*-VBTAC)/ciprofloxacin are depicted in Fig. 4. Ciprofloxacin is a

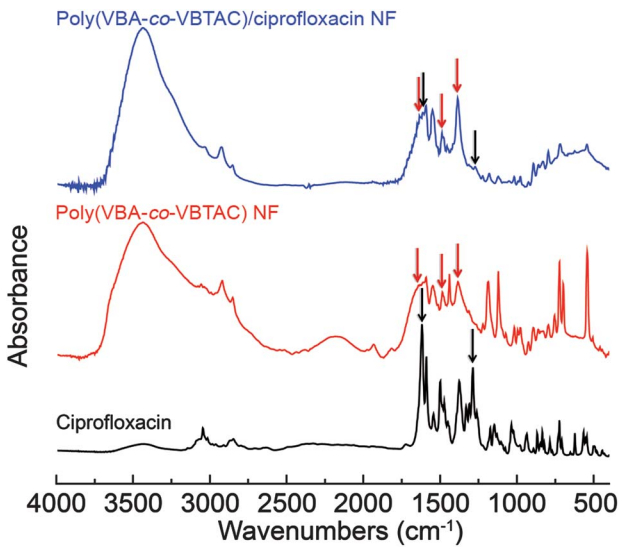

Fig. 3 FTIR spectra of ciprofloxacin, poly(VBA-*co*-VBTAC) nanofibers and poly(VBA-*co*-VBTAC)/ciprofloxacin nanofibers.

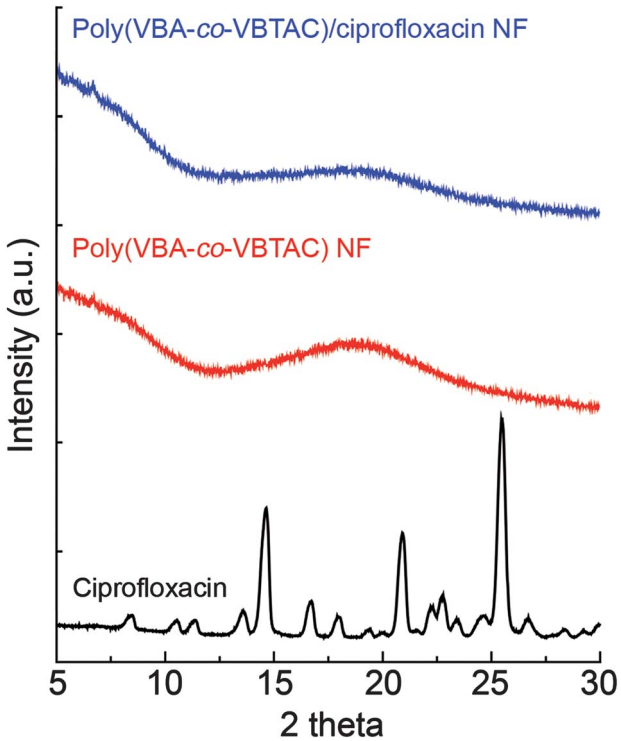

Fig. 4 XRD patterns of ciprofloxacin, poly(VBA-*co*-VBTAC) nanofibers and poly(VBA-*co*-VBTAC)/ciprofloxacin nanofibers.

crystalline material having salient peaks centered at $2\theta = 14°$, 21° and 25°. Poly(VBA-*co*-VBTAC) is an amorphous polymer showing a broad halo diffraction pattern. The absence of any diffraction peak of crystalline ciprofloxacin in the XRD pattern of poly(VBA-*co*-VBTAC)/ciprofloxacin nanofibers indicated that the ciprofloxacin molecules were distributed in the nanofibers without forming any crystalline aggregates. Rashkov *et al.* have reported crystal aggregates of ciprofloxacin hydrochloride when encapsulated in poly(L-lactide-*co*-D,L-lactide) (coPLA) or coPLA/PEG electrospun nanofibers, yet, in that study higher weight load of drugs (10–30 wt%) was used, more importantly, ciprofloxacin hydrochloride was not soluble in electrospinning solution where a milky white suspension was obtained and electrospun thereafter.[37] In our case, the ciprofloxacin was soluble in the electrospinning solution forming a homogeneous and clear solution with the polymer matrix. So, the rapid evaporation of solvent during the electrospinning process yielded amorphous dispersion of a crystalline drug in the electrospun polymeric fiber matrix as also reported for other electrospun drug–polymer nanofiber systems.[38,39] Moreover, in

our case, the hydrogen bonds between the drug molecules and the polymer matrix possibly hindered the phase separation and crystal aggregation of ciprofloxacin throughout the poly(VBA-*co*-VBTAC) matrix and therefore resulted in an amorphous phase.

Drug release from pH responsive nanofibers

Ciprofloxacin is a broad-spectrum fluoroquinolone antibacterial agent used in the treatment of both Gram-positive and Gram-negative microorganisms. Ciprofloxacin was chosen as a model drug for investigating the pH responsive release ability of electrospun poly(VBA-*co*-VBTAC) nanofibers. The loading efficiency of nanofibers loaded with 5% (w/w, with respect to polymer) ciprofloxacin was determined to be 93.4 ± 3.4%. Fig. 5 shows the cumulative drug release (%) from poly(VBA-*co*-VBTAC) pH responsive nanofibers encapsulating ciprofloxacin into three different release media having different pH values; acetate buffer solution (pH = 5.2), phosphate buffered saline (pH = 7.4) and tris-buffered saline (pH = 8.8). Two stages of release can be distinguished in the release profiles; after a quick initial release which continued for 30 minutes, the following time interval showed sustained release of ciprofloxacin from a nanofibrous matrix up to 240 minutes for acetate buffer solution and 480 minutes for phosphate buffered saline and tris-buffered saline. No further drug release was observed after 240 minutes into acetate buffer solution; whereas after 480 minutes no more drug was released into phosphate buffered saline and tris-buffered saline.

It is a known fact that the release of a drug from a polymeric matrix is mainly controlled by diffusion of the drug and/or degradation of the matrix. The observed drug release was attributed mainly to the diffusion or permeation of drug through the polymer matrix. Since the time period of our experiment (720 minutes) is not long enough to observe degradation of polymer. In addition, as seen from the SEM images of nanofibers taken after release experiment (Fig. 6), the fiber morphology of the poly(VBA-*co*-VBTAC) was retained after the release experiments were carried out in acetate buffer solution, phosphate buffered saline and tris-buffered saline.

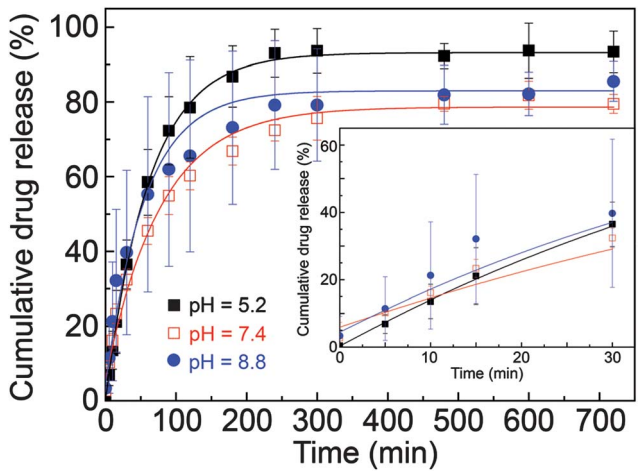

Fig. 5 Release profiles of ciprofloxacin from poly(VBA-*co*-VBTAC)/ciprofloxacin nanofibers in acetate buffer solution (pH = 5.2), phosphate buffered saline (pH = 7.4) and tris-buffered saline (pH = 8.8).

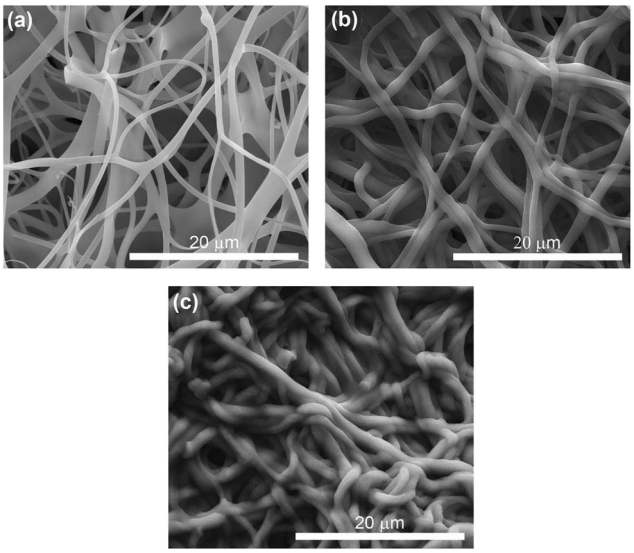

Fig. 6 The representative SEM images of poly(VBA-*co*-VBTAC)/ciprofloxacin nanofibers after release experiment; (a) acetate buffer solution (pH = 5.2), (b) phosphate buffered saline (pH = 7.4) and (c) tris-buffered saline (pH = 8.8).

The release behaviors of drug are closely related to the distribution of the drug within the matrix. Moreover, the solubility and compatibility of the drug in the drug–polymer–solvent system is of great importance in the release behavior of drugs from polymeric nanofibers. Therefore, when the drug is hydrophilic and the polymer is hydrophobic or *vice versa*, and/or the drug is not soluble in electrospinning solution, most of the drug will be localized near the surface of nanofibers due to the phase separation and lack of the sufficient physical interaction between the drug and the polymer matrix. This situation leads to quite high initial burst release.[40,41] However, in our case both ciprofloxacin and poly(VBA-*co*-VBTAC) are hydrophobic, so they are compatible; and ciprofloxacin is soluble in DMF–acetic acid (7/3) solution. Therefore, initial burst release was not so high. This may be due to the increasing intermolecular and/or intramolecular interactions. An initial burst release is required for the delivery of antibiotic drugs aiming to prevent bacterial proliferation at the initial stage; whereas, for a few organisms that manage to survive, sustained release is also needed for antibiotics.[41] Here, the sustained release of ciprofloxacin was observed as well. The total release amount of ciprofloxacin from nanofibers was more in acetate buffer solution compared to phosphate buffer saline and tris-buffered saline. The poly(VBA-*co*-VBTAC) includes cationic VBTAC units and pH-responsive VBA units. This might be due to the weak electrostatic interaction between VBA and VBTAC units at lower pHs which are below the pK_a. In our previous study, we showed that the pK_a of poly(VBA-*co*-VBTAC) polymer brushes on silicon wafer surfaces was 7.65.[33] On the other hand, Gabaston *et al.* and Liu and Armes reported that the pK_a value of VBA homopolymer was 4.4 and 7.1, respectively.[42,43] The total release amount of ciprofloxacin from nanofibers was decreased with increasing pH,

because of the increasing electrostatic interactions. The remaining ciprofloxacin content in nanofibers may originate from this interaction as well. In brief, our electrospun poly(VBA-*co*-VBTAC) nanofibers encapsulating ciprofloxacin could present a rapid enough release for bacteria not to proliferate at first stage but could provide a sustained release as well owing to the diffusion mechanism dominating in release of ciprofloxacin from nanofibers.

Conclusions

In conclusion, pH-responsive poly(VBA-*co*-VBTAC) nanofibers encapsulating ciprofloxacin were successfully prepared *via* electrospinning techniques for the purpose of controlled drug release systems. SEM imaging proved that the electrospinning of nanofibers from poly(VBA-*co*-VBTAC) was successful and encapsulation of ciprofloxacin did not affect the morphology of the nanofibers where a bead-free and smooth fiber morphology was observed for both poly(VBA-*co*-VBTAC) and poly(VBA-*co*-VBTAC)/ciprofloxacin nanofibers. The presence of ciprofloxacin in the poly(VBA-*co*-VBTAC) nanofibers was confirmed by FTIR spectroscopy. XRD data suggested that ciprofloxacin was homogeneously distributed within the poly(VBA-*co*-VBTAC) nanofibers without forming phase separated crystalline aggregates. Results of *in vitro* release experiments suggested that the poly(VBA-*co*-VBTAC)/ciprofloxacin nanofibers were capable of effectively delivering ciprofloxacin in a controlled fashion with prolonged duration depending on the pH. The initial burst release was higher with increasing pH values, because of the increasing intermolecular and/or intramolecular interactions. However, the total release amount of ciprofloxacin from nanofibers was more in acetate buffer solution compared to higher pH values. This pH-responsive poly(VBA-*co*-VBTAC) nanofibers may provide opportunities to develop innovative responsive materials for various applications. For instance, our newly developed pH responsive nanofibers may be potentially useful for controlled drug delivery and biomedical engineering.

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