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Ester prodrug-loaded electrospun cellulose acetate fiber mats as transdermal drug delivery systems

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Abstract Cellulose acetate (CA) fibers loaded with the ester prodrugs of naproxen, including methyl ester, ethyl ester and isopropyl ester, were prepared through electrospinning using acetone/*N*,*N*-dimethylacetamide(DMAc)/ethanol (4:1:1, v/v/v) as solvent. The chemical and morphological characterizations of the medicated fibers were investigated by means of SEM, DSC, XRD and FTIR, as well as the studies of the drug release properties. The results indicated that the morphology and diameter of the fibers were influenced by the concentration of spinning solution, applied voltage, electrospun solvent and the surfactants. The average diameters of the fibers ranged between 100 and 500 nm for three prodrugs. There was good compatibility between CA and three prodrugs in the blended fibers, respectively. In vitro release indicated that constant drug release from the fiber was observed over 6 days. The prodrugs were successfully encapsulated into the fibers, and this system was stable in terms of effectiveness in release.

1 Introduction

Dermal drug delivery has been gaining increasing popularity since it offers many advantages over more conventional treatments, such as accessibility, safety, non-invasiveness, compliance and effectiveness [1]. Development of the efficient means of topical delivery can increase local soft-tissue and joint-drug concentrations while reducing the systemic distribution of a drug, thereby offsetting certain limitations of its oral use [2, 3]. However, the dermal drug transport is greatly limited by the unfavorable physicochemical properties of many drugs and the efficient barrier function of the skin, and is frequently insufficient for medical uses. This limitation has led to the development of various strategies to enhance drug-skin permeation, such as the prodrug approach with the aim of changing pharmaceutical character of the parent drug and thereby enhancing its skin permeation, efficacy and therapeutic value [4, 5].

Electrospinning is one of the simplest and most effective methods for producing fibers in microscale to nanoscale. A polymer solution, when electrostatically charged, can produce non-woven polymeric fibers in desired size ranges by controlling the physical properties of the polymer solution and the spinning process parameters [6]. Due to the high surface area to volume or mass ratio of the obtained fibers, these fibrous materials have been applied in biomedical applications such as wound healing [7, 8], tissue engineering [9–11], and drug delivery [12–16]. Now many synthetic and natural biopolymers have been electrospun into ultrafine fibers. However, electrospinning of some natural biopolymers is still a challenge, such as cellulose [13, 17–20].

Cellulose, the most abundant natural resource on earth, is categorized as a linear polysaccharide. It has many advantages such as its biocompatibility, biodegradability and regenerative property, for which reason cellulose is widely used in packaging, textiles industries, and biomedical material fields [21, 22]. Fabrication of ultrafine

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native cellulose fibers by electrospinning has drawn great attention in recent years. Among various applications, electrospun CA fiber mats have been developed as carriers for transdermal delivery of drugs. Taepaiboon et al. [15] developed electrospun CA fiber mats as carriers for transdermal delivery of retinoic acid and α-tocopheral from CA solutions in 2:1 v/v acetone/DMAc containing retinoic acid and α-tocopheral. Electrospun CA fiber mats as carriers for transdermal delivery of four different nonsteroidal antiinflammatory drugs (NSAIDs), naproxen, indomethacin, ibuprofen and sulindac, were reported by Tungprapa et al. [16], who used CA solutions in 2:1 v/v acetone/DMAc as the base spinning solutions. Recently, Suwantong et al. [23] reported the CA fiber mats as carriers for the transdermal delivery of curcumin, a herbal compound found in the plant *Curcuma longa* L., by electrospinning CA solutions in 2:1 v/v acetone/DMAc containing curcumin in various amounts.

Naproxen (Fig. 1a) is an interesting nonsteroidal antiinflammatory drug (NSAID) that has been widely used for the treatment of dermatitis, rheumatic diseases and the pain relief. Unfortunately, following topical administration in man naproxen shows bioavailability of only 1–2% which may be attributed to ionizable carboxylic acid group [24]. Therefore, various prodrugs have been studied in attempt to increase the dermal permeation of naproxen by transiently masking its ionized group. Recently, both penetration enhancers and the prodrug approach have been used to increase the percutaneous absorption of naproxen. The researchers already found that the naproxen ester prodrugs can promote the transdermal absorption of naproxen, and their metabolism catalyzed by skin esterase is stereoselective in the percutaneous penetration process [25–29]. In this study, the electrospinning process of CA in a range from 5% to 20% (w/v) was investigated in a mixture solvent acetone/*N*,*N*-dimethylacetamide (DMAc)/ethanol (4:1:1, v/v/v), containing naproxen methyl ester (NME) 5% based on the weight of CA powder, as well as the influence of the applied voltage and the surfactants. Then the uniform and smooth fiber mats of CA loaded with the ester prodrugs of naproxen, including methyl ester, ethyl ester and isopropyl ester, were prepared by electrospinning in the optimal conditions. The chemical and morphological characterizations of the medicated fibers were investigated by means of SEM, DSC, XRD and FTIR. The results indicated that there was good compatibility between CA and the ester prodrugs of naproxen in the blended nanofibers. The in vitro release experiment of the medicated fiber mats was also carried out in the medium of physiological saline, and the results indicated that sustained drug release from the fiber mats was observed for a long duration of time (over 6 days).

2 Experimental

2.1 Materials and chemicals

Naproxen was purchased from an international pharmaceutical factory (Shanghai, China). Cellulose acetate (CA, white powder; $M_W = 100\ 000$ Da) was purchased from *Acros*, and used as received. Sodium dodecyl sulfate (SDS), cetyltrimethyl ammonium bromide (CTAB) and Triton X-100 were purchased from Sinopharm Chemical Reagent Co, Ltd. (SCRC, Shanghai, China), and used as received. Methyl ester, ethyl ester and isopropyl ester of naproxen were prepared and purified according to literature procedures (Fig. 1b, c, d) [30]. All other chemicals were used as received without further purification.

2.2 Preparation of the spinning solutions

Cellulose acetate solution with concentration of 5, 8, 10, 15 and 20% (w/v) were prepared by dissolving the appropriate amounts of cellulose acetate into acetone/DMAc/ethanol (4:1:1, v/v/v) mixture solvent, respectively. The quantity of methyl ester, ethyl ester and isopropyl ester of naproxen were 5% based on the weight of CA powder added into the spinning solution, respectively. Prior to electrospinning, the solutions were stirred at room temperature until the CA was completely dissolved, and then degassed with an ultrasonator (59 Hz, 350 W, Shanghai Jinghong Instrument Co., Ltd., Shanghai, China) for 30 min to obtain the homogeneous co-dissolved spinning dopes. When an additional

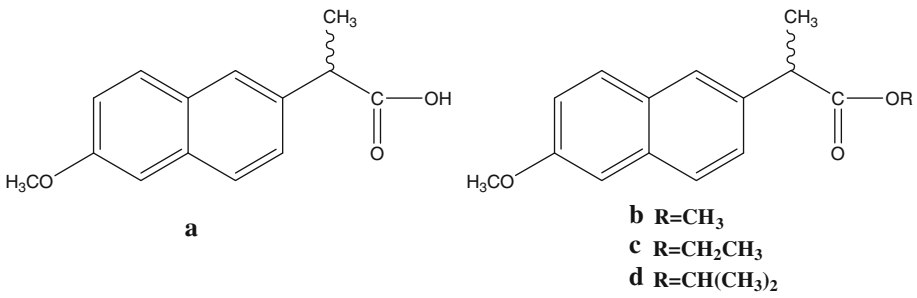

Fig. 1 Chemical structure of naproxen (**a**) and naproxen ester prodrug (**b–d**)

surfactant was used, such as SDS, CTAB and Triton X-100, the material was added at 1% the amount of polymer.

2.3 Preparation of neat and prodrug-loaded CA or PLGA/CA fiber mats

In the electrospinning process, a high electric potential was applied to a droplet of the spinning solution at the tip (diameter 0.45 mm) of a syringe needle. The electrospun fibers were collected on aluminium foil which was placed at a distance of 15 cm from the syringe tip. A power supply (ZGF60 kV/2 mA, Soute., Ltd., China) was used at different voltage of 8, 10, 12.5 and 15 kV. The feeding rate of the spinning solution was controlled at 1.0 ml/h by means of a syringe pump (Cole-Parmer®, USA). All electrospinning processes were performed at room conditions (Temperature was 24 ± 1°C and relative humidity was 68 ± 3%). The electrospun fibers were further dried at 40°C under vacuum (320 Pa) in a DZF-6050 Electric Vacuum Drying Oven (Shanghai Laboratory Instrument Work Co. Ltd., China) to facilitate the removal of residual organic solvents and moisture.

2.4 Characterization of neat and prodrug-loaded CA or PLGA/CA fiber mats

Scanning electron microscope (SEM, JEOL, JSM-5600LV) was used to investigate the macroscopic morphology/surface texture of the electrospun fibers. FTIR spectra were collected on Nicolet-Nexus 670 spectrometer (Nicolet Instrument Corporation Madison, USA) in KBr form. The differential scanning calorimetry (DSC) analysis was carried out using an MDSC 2910 differential scanning calorimeter (TA Instruments Co., USA). Sealed samples were heated at 10°C/min from 20 to 250°C, and the nitrogen gas flow rate was 40 ml/min. The wide-angle X-ray diffractograms (XRD) were obtained on a D/Max-BR diffractometer (Rigaku, Japan) with Cu K_α radiation in the 2θ range of 5°–60° at 40 mV and 300 mA.

2.5 Release of prodrug from prodrug-loaded CA fiber mats

The actual content of methyl ester, ethyl ester and isopropyl ester of naproxen in the prodrug-loaded fibers were quantified by dissolving each sample in a mixture of acetone/DMAc (2:1, v/v) and measuring them in a UV–vis spectrophotometer (UV-2102PC Unico, Shanghai, China) at 330 nm. The amount of methyl ester, ethyl ester and isopropyl ester of naproxen in the fibers was back-calculated from the obtained data against a predetermined calibration curve for the drugs.

The in vitro release characteristic of methyl ester, ethyl ester and isopropyl ester of naproxen from the prodrug-loaded CA fibers was investigated by using a drug release instrument (Tianjin RCZ-8A dissolution apparatus, Tianjin, China). Due to investigating the in vitro release prodrug-loaded fibers on the skin surface, physiological saline (0.9%) was used as the releasing medium. Prodrug-loaded fibers were weighed and placed in releasing medium (600 ml) at 32 ± 0.5°C and the instrument was set at 50 rpm. At appropriate time intervals, a 5 ml of the release medium was withdrawn and an equal amount of the fresh medium was refilled. The amount of NME in the sample solutions was determined using UV spectrophotometer at the wavelength of 330 nm. The obtained data were calculated to determine the cumulative amount of methyl ester, ethyl ester and isopropyl ester of naproxen released from the specimens at each time point. The experiments were carried out in triplicate and the results were reported as average values.

3 Results and discussion

3.1 Effect of concentration of the spinning solution

The morphology and diameter of electrospun nanofibers are dependent on the various parameters such as solution concentration, applied voltage, and elecrospinning distance and so on [31]. The concentration or the corresponding viscosity of the electrospinning solution was determined to be one of the most effective variables in controlling the fiber morphology and diameter [32].

Figure 2 shows SEM images of the medicated fiber mats as a function of the spinning concentration. The CA solutions were prepared at five different concentrations of 5, 8, 10, 15 and 20% (w/v) containing 5% NME based on the weight of CA powder. It was found that the morphology of the fibers changed gradually from the more beaded structures to a uniform fiber-structure with increasing concentration of the spinning solution, and the average diameter of the fibers increased with increasing the concentration (from 100–200 nm to 1–2 μm). Obviously, Figs. 2a and b showed that there were some undesirable forms of fibers, such as beads on fiber strings, notches and local non-uniformity in the thickness of the nanofibers, due to the non-optimization of the experimental conditions. Fortunately, Fig. 2c got the fine and continuous morphology and structure of the fibers by increasing the spinning concentration. However, when the spinning concentration of CA was increased further than 15%, the fibers had oversized diameters and were linked up together (Fig. 2d, e). Thus the optimal concentration of the spinning solution was selected as 10% (w/v) for further electrospinning process. In order to improve the electrospinnability of CA, a cosolvent, ethanol, was added to the

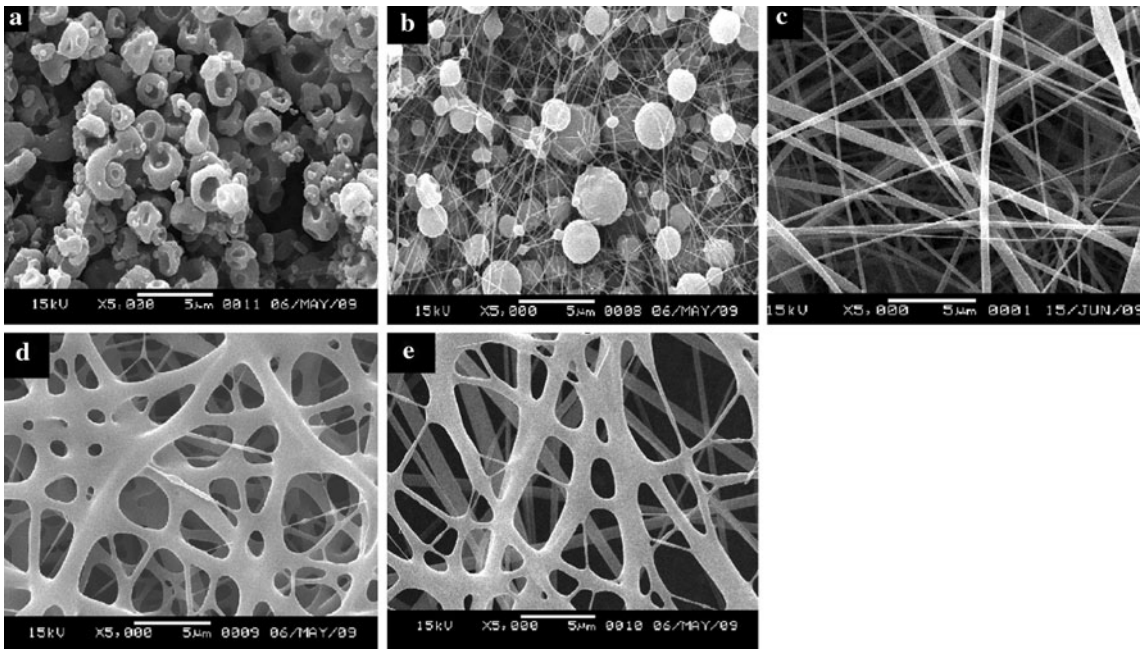

Fig. 2 SEM images of the medicated fiber mats with concentration of **a** 5%, **b** 8%, **c** 10%, **d** 15%, **e** 20% (w/v) (voltage, 12.5 kV; 5% naproxen methyl ester)

acetone/DMAc mixture solvent at a specific mass ratio to decrease the viscosity and surface tension of the solutions.

3.2 Effect of applied voltage

The effects of applied voltage on fiber morphology and diameter were also detailedly investigated. Fig. 3 shows SEM images of the fibers at different applied voltages (i.e., 8, 10, 12.5, 15 kV) by electrospinning a 10% CA solution, containing 5% NME based on the weight of CA powder. The results indicated that the fibers with finer and uniform morphology and structure were obtained with increasing applied voltage, and this is consistent with the results obtained by changing the spinning solution. Beads were generated by electrospinning the mixture solution at the applied voltage below 12.5 kV, suggesting that the applied voltage was too low to ensure enough interactions among CA molecules for fabricating smooth nanofibers. Furthermore, the morphology similar to the crosslinkings among the fibers appeared at higher voltage than 20 kV. As we know that the presence of more beads and crosslinkings in the nanofibers would have no positive influence on properties of surface area and mechanical performance, so the suitable applied voltage was selected at 12.5 kV for further electrospinning process.

3.3 Effect of surfactants

Electrospinning and the obtained fiber mats could be affected by adding a surfactant to the polymer solution, since the surfactant could have an influence on the electrostatic or rheological properties of the polymer solution. Yao et al. [33] has reported that a small amount of non-ionic surfactant, Triton X-100, in aqueous polyvinyl alcohol, improved both the onset voltage and the reproducibility of electrospinning. Lin et al. [34] found that the addition of cationic surfactants, DTAB and TBAC, effectively stopped the formation of beaded fibres during the electrospinning of polystyrene.

Figure 4 shows SEM images of the medicated fiber mats after the addition of different surfactants (1%) to the spinning solution, including a cationic surfactant SDS, an anionic surfactant CTAB and a non-ionic surfactant Triton X-100. More or less beads-on-string structures emerged in the spun fiber mats, from a CA solution without the presence of any surfactant. As shown in Fig. 4d, the beaded fiber covered some parts of the electrospun area without the addition of the cosolvent ethanol and any surfactant. When a small amount of SDS was added in the polymer solution, the same electrospinning process produced non-beaded fiber mats. The SEM images shown in Fig. 4a revealed that the addition of the surfactants led to bead-free and homogeneous fiber mats.

In order to confirm the charge effect of cationic surfactant on the elimination of beaded fibers, a similar electrospinning process was also conducted by replacing the cationic surfactant with a anionic surfactant, CTAB and a non-ionic surfactant, Triton X-100. As shown Fig. 4b and c, the addition of CTAB and Triton X-100 did not totally reduce the formation of beaded fibers. The addition of

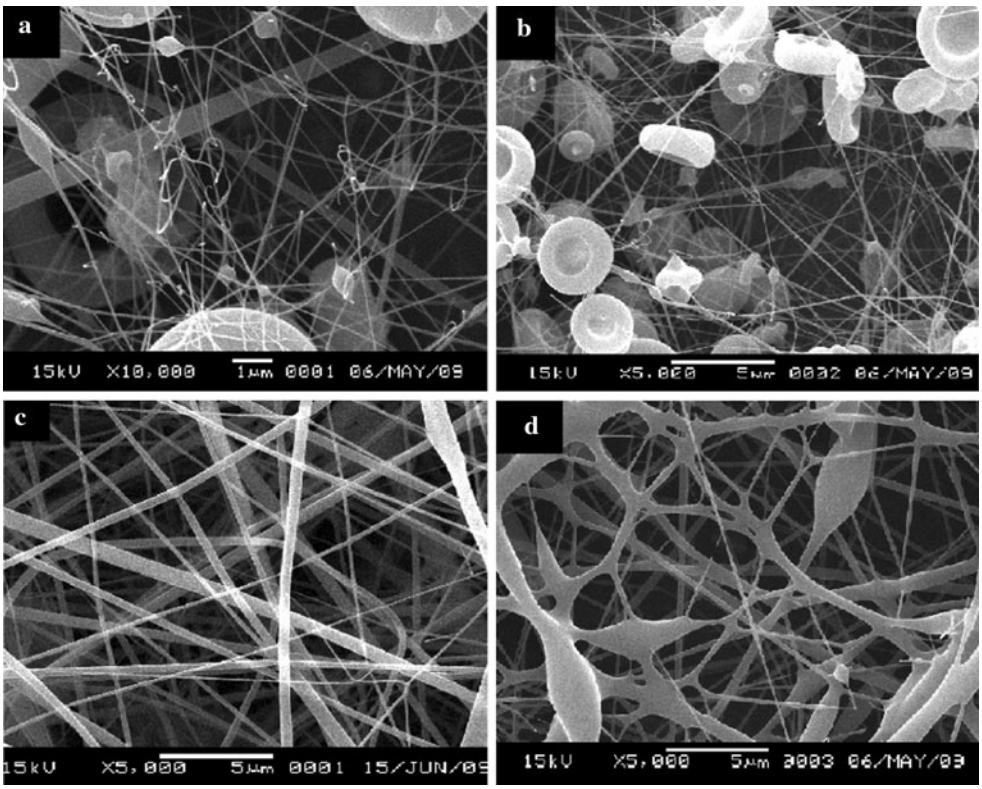

Fig. 3 SEM images of the medicated fiber mats at different applied voltage: **a** 8 kV, **b** 10 kV, **c** 12.5 kV, **d** 15 kV (concentration, 10% CA and 5% naproxen methyl ester)

CTAB and Triton X-100 could lead to some decrease in the surface tension, but had no apparent influence on the viscosity of the solution. In addition, the morphology of the fiber mats obtained in the presence of two ionic surfactants, SDS and CTAB, which showed more regular structures and more uniform diameters, was different from those without the surfactant. Furthermore, the strength of the interaction between the polymer and surfactant depends on the polymer, the surfactant, the solvent and their relative concentration. A strong interaction could alter the rheological properties of the polymer solution. The results also showed that there was stronger interaction between the cationic surfactant SDS and the polymer CA than other two surfactants in the spinning solution.

Fortunately, efforts to eliminate the beaded fibers by adjusting the operating conditions and changing the polymer concentrations were also successful as it mentioned before, apart from the addition of the surfactants to the spinning solution (Fig. 5). The medicated fiber mats loaded with NME, naproxen ethyl ester (NEE) and naproxen isopropyl ester (NIE) appeared smooth and uniform, and there were little drug crystals detected on the polymer surface. Average diameters of 200 ± 85, 210 ± 101, and 250 ± 150 nm were obtained for them, respectively. This indicated that methyl ester, ethyl ester and isopropyl ester of naproxen were well embedded in the CA fibers, and that the drugs dissolved completely in the mixture solvent.

3.4 Characterization of the medicated nanofibers

3.4.1 FTIR analysis

Besides new created functional group by chemical reaction between polymers, the intermolecular interactions can also be characterized by FTIR. Figure 6 gives FTIR spectra of the medicated fibers of three naproxen ester prodrugs, cellulose acetate and three naproxen ester prodrugs, respectively.

Basically, the medicated fibers of three naproxen ester prodrugs exhibited a number of main absorption peaks at 3451, 1752, 1634, 1372, 1237 and 1051 cm^{-1}, respectively. Their spectra are quite consistent with the main functional groups of CA and their corresponding naproxen ester prodrugs, though the positions of characteristic absorption bands are shifted to a longer waveband. The result indicates that the chemical integrity of the as-loaded-prodrugs was maintained after the electrospinning process, and there is good compatibility between CA and three naproxen ester prodrug molecules in the blended fiber mats, respectively.

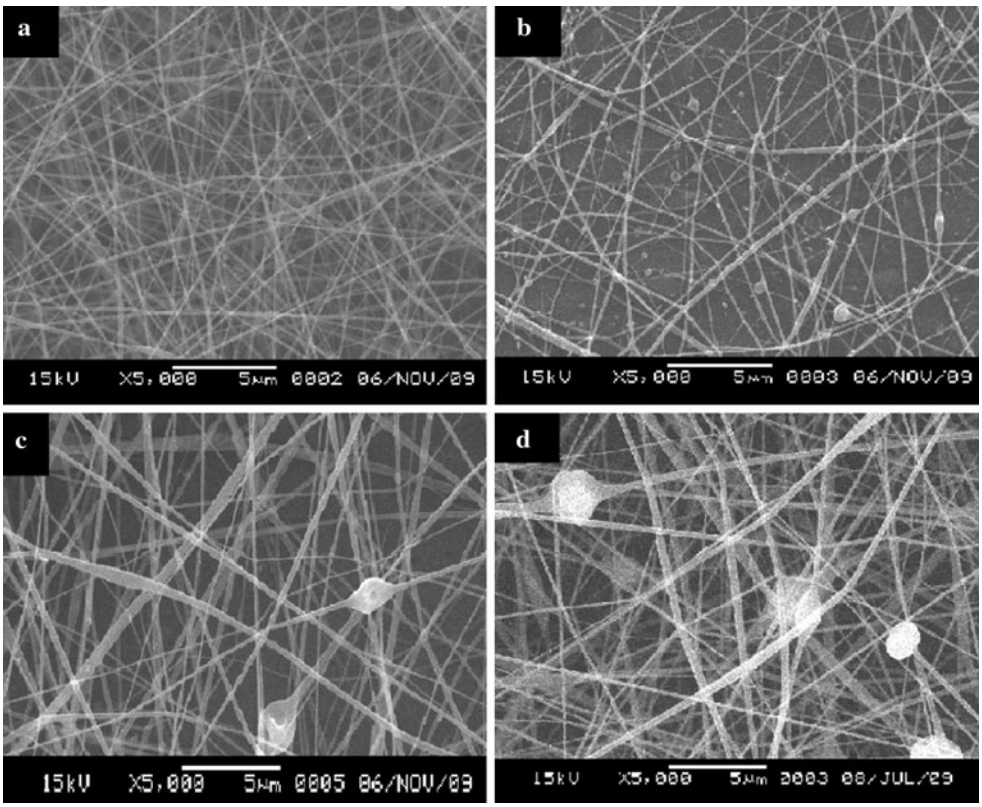

Fig. 4 SEM images of the medicated fiber mats adding 1% different surfactants: **a** SDS, **b** CTAB, **c** Triton X-100 (concentration, 10% CA and 5% naproxen methyl ester; voltage, 15 kV; acetone/DMAc, 2:1), **d** control (acetone/DMAc, 2:1)

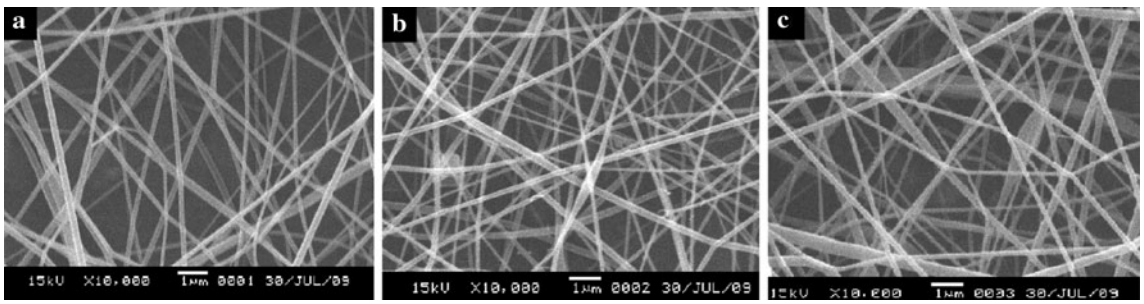

Fig. 5 SEM images of the medicated fiber mats loaded with naproxen methyl ester (**a**), naproxen ethyl ester (**b**), naproxen isopropyl ester (**c**), respectively

3.4.2 X-ray diffraction patterns analysis

XRD patterns of the electrospun medicated fiber mats, powders of NME and the electrospun CA fiber mats are displayed in Fig. 7. It was shown that the electrospun CA fiber mats were amorphous as denoted by the absence of a characteristic diffraction peak (Fig. 7c). However, NME was present as a crystalline material with many characteristic diffraction peaks, mainly appearing at a diffraction angle of 2θ at 6.08, 24.72, 31.06 (Fig. 7b).

The crystalline NME was not detected in the electrospun medicated fiber mats, and characteristic hump of amorphous forms appeared (Fig. 7a), indicating that NME was no longer present as a crystalline material, but was fully converted into the amorphous state. Furthermore, NME existed in the electrospun medicated fiber mats as the amorphous state, also illustrating there was not any chemical reaction or intermolecular action between polymer and drugs. There was good compatibility between CA and three naproxen ester prodrugs molecules in the blended fiber mats, respectively, and

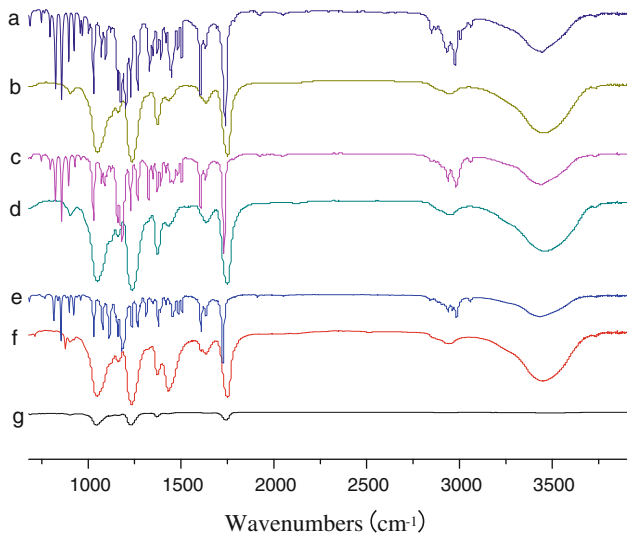

Fig. 6 FTIR spectra of the nanofibers: (*a*) naproxen methyl ester (NME), (*b*) medicated fibers loaded with NME, (*c*) naproxen isopropyl ester (NIE), (*d*) medicated fibers loaded with NIE, (*e*) naproxen ethyl ester (NEE), (*f*) medicated fibers loaded with NEE, (*g*) CA

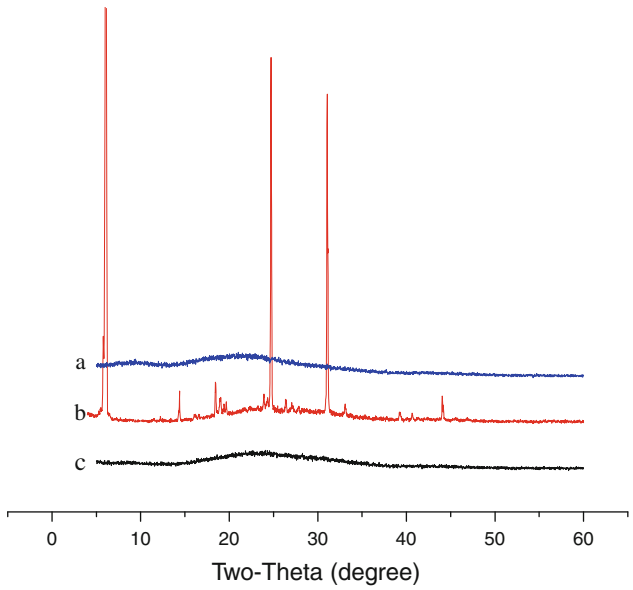

Fig. 7 X-ray diffraction patterns of the nanofibers: (*a*) medicated fibers loaded on CA, (*b*) naproxen methyl ester, (*c*) CA

the results were consistent with those obtained from FTIR.

3.4.3 DSC analysis

DSC thermograms of the electrospun fiber mats with or without NME are shown in Fig. 8. The bicomponent fiber mats with uniform structure can be obtained by increasing the proportion of PLGA/CA (not listed). It can be seen from the thermogram of pure NME that clear melting

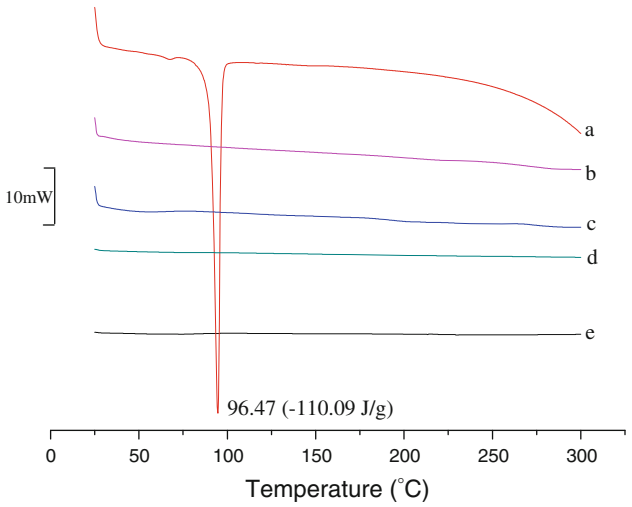

Fig. 8 DSC thermograms of the fiber mats: (*a*) naproxen methyl ester, (*b*) medicated fibers loaded on PLGA/CA, (*c*) PLGA/CA, (*d*) medicated fibers loaded on CA, (*e*) CA

endothermic peak appears around 96.47°C and the enthalpy is 110.09 J/g (Fig. 8a). There is no clear melting endothermic peak in thermogram of either the CA or PLGA/CA fibers, apart from a weak broad endotherm due to the dehydration with a peak at 66.17C and 50.12°C, respectively (Fig. 8c, e).

DSC thermograms of the medicated fibers loaded on PLGA/CA and CA (Fig. 8b, d) showed no any melting endothermic peak of the drug and an unapparent broad endotherm of dehydration. These phenomena were ascribed to the addition of the drug into the electrospun polymer fibers, and indicated that NME was no longer present as a crystalline material, but is converted into the amorphous state, and that the NME molecules may influence the dehydration of the polymers.

All the results obtained from DSC were consistent with those from FTIR and XRD, adequately illustrating that the physical status of naproxen ester prodrugs in the electrospun medicated CA fiber mats was amorphous, which were very useful for improving dissolution profiles of the unsolvable drugs.

3.5 In vitro drug release

The drug release profiles of NME, NEE and NIE from the prodrug-loaded fibers are shown in Fig. 9, respectively. Here, the cumulative release profiles of the naproxen ester from the prodrug-loaded fibers were reported in the manner, i.e., as the percentage of the weight of the naproxen ester released divided by the actual weight of it in the specimens. It was found that the prodrug-loaded fibers specimens showed a gradual increase in the amount of the naproxen ester released from the fibers.

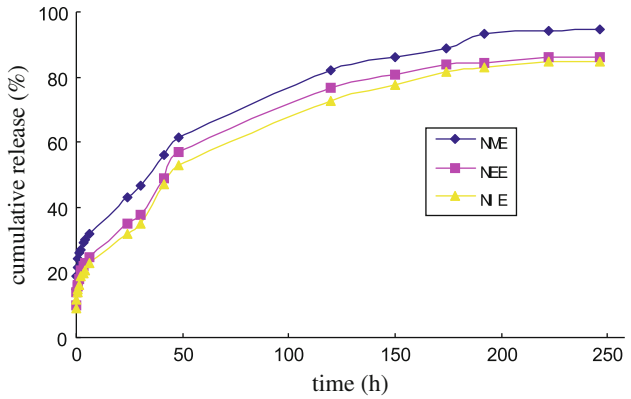

Fig. 9 Cumulative release profiles of naproxen methyl ester (*NME*), naproxen ethyl ester (*NEE*) and naproxen isopropyl ester (*NIE*) from the prodrug-loaded fibers

It could be seen from the slope of the curve that the release was greatest during the initial part of the process, as naproxen ester molecules adsorbing or loosely binding near the surface of the fibers was quickly diffused in buffer solution. However, it is probably because the ester molecules being encapsulated in the inner core of the fiber matrix, would need a long distance to diffuse through and take longer time to be released, so the slope of the release curve became smaller gradually. In the followed 150 h, all three samples took on a sustained release phase probably due to the decline of the diffusion driving force induced by the reduction of the drug molecules inside the inner space. The release behaviour mainly depended on polymer matrix degradation and drug diffusion. It was obvious that the release processes were not complete, and rest of them would release with the degradation of polymer fibers. Moreover, the drug diffusion of NME was faster than the other naproxen esters due to their different molecular weight, solubility, and compound polarity and so on.

4 Conclusions

Herein, a new system for the delivery of naproxen as nonsteroidal antiinflammatory drug (NSAID) was developed based on the encapsulation of three ester prodrugs of naproxen in the electrospun CA fiber mats. The medicated fiber mats loaded with NME, NEE and NIE appeared smooth and uniform, and there were few drug crystals detected on the fiber surface. The results from FTIR, XRD, DSC and SEM demonstrated that three ester prodrugs of naproxen had good compatibility with CA and were able to distribute uniformly within the polymer fiber matrix. The morphology and diameter of the fibers were influenced by concentration of spinning solution, applied voltage and the electrospun solvent, and the more consistent structures were obtained by adding the ionic surfactant SDS to the spinning solution. The drug release behaviour was mainly related with the drug-polymer compatibility for three ester prodrugs. The drug release was rapid at the initial period, however, a sustained release phase could be achieved over 150 h as a long duration of time. These findings demonstrated that controlled release of prodrugs from CA fibers could be potentially useful in transdermal drug delivery systems.

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