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Release characteristics of four model drugs from drug-loaded electrospun cellulose acetate fiber mats

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Abstract

Ultra-fine fiber mats of cellulose acetate (CA; $M_w \approx 30\,000$ Da; degree of acetyl substitution ≈ 2.4) containing four different types of model drugs, i.e., naproxen (NAP), indomethacin (IND), ibuprofen (IBU), and sulindac (SUL), were successfully prepared by electrospinning from 16% w/v CA solutions in 2:1 v/v acetone/*N*,*N*-dimethylacetamide (DMAc). The amount of the drugs in the solutions was fixed at 20 wt.% based on the weight of CA powder. The morphology of the drug-loaded electrospun (e-spun) CA fiber mats was smooth, with the average diameters of these fibers ranging between 263 and 297 nm. No presence of the drug aggregates of any kind was observed on the surfaces of these fibers, suggesting that the drugs were encapsulated well within the fibers. After submersion in the acetate buffer solution at 37 °C for 24 h, the drug-loaded e-spun CA fiber mats swelled particularly well (i.e., 570–630%), while the corresponding solvent-cast film counterparts did not. The release characteristics of the model drugs from both the drug-loaded CA fiber mats and the drug-loaded as-cast CA films were carried out by the total immersion method in the acetate buffer solution at 37 °C. At any given immersion time point, the release of the drugs from the drug-loaded e-spun CA fiber mats was greater than that from the corresponding as-cast films. The maximum release of the drugs from both the drug-loaded fiber mats and films could be ranked as follows: NAP > IBU > IND > SUL.

Keywords: Electrospinning; Ultra-fine fibers; Cellulose acetate

1. Introduction

Electrospinning (e-spinning) is a unique processing technique that can be used to fabricate ultra-fine fibers, diameters of which are in sub-micrometer down to nanometer range. In this process, a continuous strand of a polymer liquid (i.e., solution or melt) is ejected through a nozzle by a high electrostatic force to deposit randomly on a grounded collector as a non-woven fiber mat. These fibers exhibit several interesting characteristics, e.g., a high surface area to mass or volume ratio, small inter-fibrous pore size with high porosity, vast possibilities for surface functionalization, etc. [1–3]. These advantages render electrospun (e-spun) polymeric fibers good candidates for a wide variety of applications, including filters [4], composite reinforcements [5,6], carriers for topical or transdermal delivery of drugs [7–10], and scaffolds for cell and tissue culture [11–13].

Cellulose acetate (CA) is the acetate ester of cellulose. CA has been fabricated as semi-permeable membranes for separation processes and fibers and films for biomedical applications [14]. E-spinning of 5 and 8 wt.% CA solutions in acetone resulted in the formation of short and beaded fibers with diameters being ~1 μm [15]. An improvement in the e-spinning of CA was achieved with 2:1 v/v acetone/dimethylacetamide (DMAc) as the mixed solvent system [16]. This mixture allowed the resulting CA solutions (i.e., 12.5–20 wt.%) to be e-spun into fibers with diameters ranging between ~100 nm and ~1 μm. CA solutions in acetone/water mixtures (i.e., water content = 10–15 wt.%) have also been successfully fabricated into ultra-fine fibers by e-spinning [17]. Additionally, 3:1:1 v/v/v

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acetone/dimethylformamide (DMF)/trifluoroethylene (TFE) was used to prepare a CA solution that resulted in the e-spun fibers with diameters ranging from ~200 nm to ~1 μm [18].

E-spun CA fiber mats have been explored as antimicrobial [19,20] and affinity [18] membranes. The antimicrobial CA fibrous membranes [19,20] were prepared from 10 wt.% CA (M_w = 30 000 Da; acetyl content = 39.8%) solution in 80:20 w/w acetone/water containing $AgNO_3$ (i.e., 0.01–0.5% based on the weight of CA) by e-spinning [applied electrostatic field strength (EFS) = 17 kV/10 cm; polarity of emitting electrode = positive; solution flow rate = 3 ml h^{-1}]. Ag^+ ions were photo-reduced into Ag nanoparticles (average diameters = 3–21 nm) by irradiating the e-spun fibers (average diameters = 610–1910 nm) with UV light (λ_{max} = 245 or 365 nm). On the other hand, the affinity CA fibrous membranes [18] were prepared from 0.16 g ml^{-1} CA (M_w = 29 000 Da; acetyl content = 40%) solution in 3:1:1 v/v/v acetone/DMF/TFE by e-spinning (applied EFS = 25 kV/15 cm; polarity of emitting electrode = positive; solution flow rate = 4 ml h^{-1}). The membranes were subsequently heat-treated at 208 °C for 1 h and later treated in 0.1 M NaOH solution in 4:1 v/v water/ethanol for 24 h to obtain regenerated cellulose (RC) membranes. Cibacron Blue F3GA, a sulfonated triazine dye, was then coupled onto the surface of the RC membranes. The capture capacity of the membranes towards bovine serum albumin (BSA) was reported to be ~13 mg g^{-1}.

As mentioned, a great deal of e-spun polymeric fiber mats has been developed as carriers for topical or transdermal delivery of drugs [7–10]. Recently, we reported the preparation of poly(vinyl alcohol) (PVA; degree of polymerization ≈ 1600; degree of hydrolysis = 97.5–99.5%) fiber mats containing four different types of model drugs (sodium salicylate, diclofenac sodium, naproxen, and indomethacin) by e-spinning (applied EFS = 15 kV/15 cm; polarity of emitting electrode = positive; solution flow rate = 1 ml h^{-1}) [10]. The release characteristics of the drugs from the fiber mats were compared with those from the corresponding solvent-cast films and the results indicated that the drug-loaded e-spun fiber mats exhibited much better release characteristics of the model drugs than the drug-loaded as-cast films. On the other hand, CA in the form of solvent-cast membranes has been explored as carriers for the delivery of scopolamine base [21] and chlorhexidine gluconate, indomethacin, and meloxicam [22], while CA in the form of e-spun fibrous membranes has been explored as carriers for the delivery of vitamin A acid (all-*trans* retinoic acid) and vitamin E (α-tocopherol) [23].

In the present contribution, mats of ultra-fine CA fibers were prepared by e-spinning and these e-spun fiber mats were explored as topical drug-delivery carriers. Four types of non-steroidal anti-inflammatory drugs (NSAIDs), i.e., naproxen, indomethacin, ibuprofen, and sulindac (with varying solubility in water), were incorporated in the e-spun CA fiber mats. Morphology and thermal property of the neat and the drug-loaded e-spun fiber mats, chemical integrity of the drugs within the drug-loaded e-spun fiber mats, swelling and weight loss behavior of the neat and the drug-loaded e-spun fiber mats in an aqueous medium, and release characteristics of the drugs from the drug-loaded e-spun fiber mats were investigated by total immersion method. Comparisons were made against the corresponding solvent-cast films.

2. Experimental details

2.1. Materials

Cellulose acetate (CA; white powder; M_w ≈ 30 000 Da; acetyl content = 39.7 wt.%; degree of acetyl substitution ≈ 2.4) was purchased from Sigma-Aldrich (Switzerland). Naproxen (NAP) and indomethacin (IND) were donated from Pharmasant Laboratories (Thailand). Ibuprofen (IBU) and sulindac (SUL) were purchased from Sigma-Aldrich (Switzerland). These drugs are used in the symptomatic management of painful and inflammatory conditions. The chemical structure for each of these model drugs is shown in Fig. 1 [24]. Acetone (Carlo Erba, Italy), *N*,*N*-dimethylacetamide [DMAc, Labscan (Asia), Thailand], sodium acetate (Ajax Chemicals, Australia), and glacial acetic acid (Merck, Germany) were of analytical reagent grade and used without further purification. Table 1 summarizes some of the important information (i.e.,

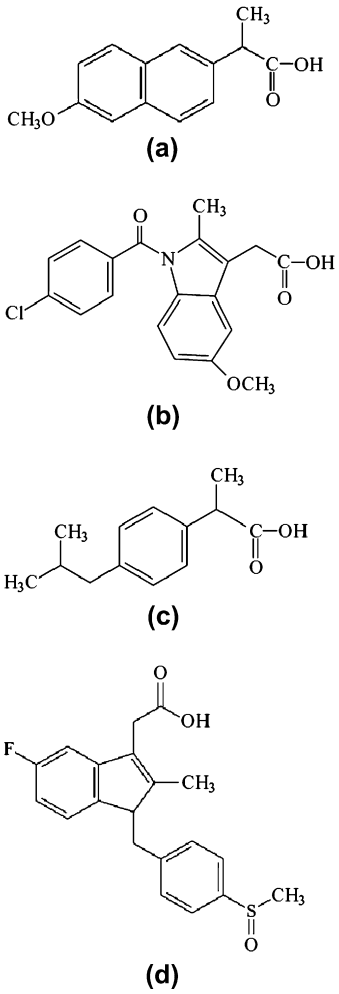

Fig. 1. Chemical structure of (a) naproxen (NAP), (b) indomethacin (IND), (c) ibuprofen (IBU), and (d) sulindac (SUL).

Table 1
Molecular mass, melting temperature, solubility parameter, and pK_a for cellulose acetate and the model drugs

Material	Molecular mass (g mol^{-1})	Melting temperature (°C)	Solubility parameter (J cm^{-3})$^{1/2}$	Water solubility (mg L^{-1})	pK_a
Cellulose acetate (CA)	30 000	227–230	25.1	–	–
Naproxen (NAP)	230.3	153	21.0	15.9	4.15
Indomethacin (IND)	357.8	158	23.9	0.937	4.50
Ibuprofen (IBU)	206.3	75–77	19.1	49.0	4.91
Sulindac (SUL)	356.4	183	24.8	Insoluble (pH < 4) 3000 (pH ≥ 6)	4.70

molecular mass, melting temperature, solubility parameter, and pK_a) of CA and the model drugs [24].

2.2. Preparation of neat and drug-loaded CA fiber mats and films

A weighed amount of CA powder was dissolved in 2:1 v/v acetone/DMAc to obtain a CA solution at a concentration of 16% w/v [25]. After that, four different types of the model drugs were individually added into the base CA solution under constant stirring for 4 h prior to e-spinning. The initial loading of the drugs was 20 wt.% (based on the weight of CA powder). Prior to e-spinning, the as-prepared solutions were measured for their shear viscosity, surface tension, and conductivity using a Brookfield DV-III programmable viscometer, a CSC Scientific tensiometer, and a Jenway 4130 conductivity meter, respectively. The measurements were carried out in triplicate at 25 °C.

E-spinning of the as-prepared solutions was carried out by connecting the emitting electrode of positive polarity from a Gamma High-Voltage Research UC5-30P high voltage DC power supply to the solutions in a standard 50-ml syringe, the open end of which was attached with a blunt gauge-20 stainless steel needle (OD = 0.91 mm), used as the nozzle, and the grounding electrode to a rotating metal drum (diameter and width ≈ 15 cm), used as the fiber-collecting device. A fixed applied electrical potential of 12 kV was applied over a fixed collection distance of 15 cm (i.e., the EFS value of 12 kV/15 cm) and the rotational speed of the drum was ~100 rpm. For morphological study, the collection time was ~10 min, while, for the rest of the experiments, it was ~24 h. Upon the completion of the e-spinning process, the e-spun fiber mats were removed from the collector and characterized as such.

For comparison purposes, the neat and the drug-loaded CA films were also prepared by solvent-casting technique from 12% w/v CA solution in 2:1 v/v acetone/DMAc and the CA solutions that contained 20 wt.% of the drugs. The thickness of both the e-spun fiber mats and the as-cast films was between 20 and 35 μm.

2.3. Characterization of neat and drug-loaded CA fiber mats and films

Morphological appearance of the neat and the drug-loaded e-spun CA fiber mats as well as that of the neat and the drug-loaded as-cast CA films prior to the drug release studies was observed by a JEOL JSM-6400 scanning electron microscope (SEM). Each of the fiber mat and the film samples was sputtered with a thin layer of gold using a Polaron Range SC7620 sputtering device prior to SEM observation. Diameters of the individual fibers within the e-spun fiber mats were measured directly from SEM images using a SemAfore 4.0 software, with the average values being calculated from at least 50 measurements.

A Bruker Advanced DPX ^{1}H nuclear magnetic resonance spectrometer (^{1}H NMR) was used to investigate the chemical integrity of the model drugs in the drug-loaded e-spun CA fiber mats (each sample weighed 2–3 mg), using deuterated dimethylsulfoxide (DMSO-d_6) as solvent. A Perkin–Elmer DSC-7 differential scanning calorimeter (DSC) and a Perkin–Elmer Pyris 1 thermogravimetric/differential thermal analyzer (TG/DTA) were used to investigate thermal behavior of the drugs as well as the neat and the drug-loaded e-spun CA fiber mats. In DSC, each heating thermogram was conducted in the temperature range of 50–270 °C at a heating rate of 10 °C min^{-1}, while, in TG/DTA, it was conducted in the temperature range of 35–700 °C at a heating rate of 10 °C min^{-1}, all in a nitrogen atmosphere.

Degree of swelling and weight loss of both the neat and the drug-loaded e-spun CA fiber mats as well as those of the neat and the drug-loaded as-cast CA films were measured after the samples were submerged in an acetate buffer solution (see below for the preparation of the acetate buffer solution) at 37 °C for 24 h according to the following equations:

$$\text{Degree of swelling}(\%) = \frac{M - M_d}{M_d} \times 100, \quad (1)$$

and

$$\text{Weight loss}(\%) = \frac{M_i - M_d - M_r}{M_i - M_r} \times 100, \quad (2)$$

where M is the weight of each sample after submersion in the buffer solution for 24 h, M_d is the weight of the sample after submersion in the buffer solution for 24 h in its dry state, M_i is the initial weight of the sample in its dry state, and M_r is the weight of a model drug that was released from the sample.

2.4. Release of model drugs from drug-loaded CA fiber mats and films

2.4.1. Preparation of acetate buffer solution

Acetate buffer solution was chosen to simulate the physiological pH of the human skin of 5.5. To prepare 1000 ml of the

buffer solution, 150 g of sodium acetate was dissolved in about 250 ml of distilled water. Exactly 15 ml of glacial acetic acid was then added very slowly into the aqueous sodium acetate solution. Finally, distilled water was added into the solution to fill the volume and the pH value of the solution was verified by a Metrohm 744 pH-meter.

2.4.2. Actual drug content

The actual amount of the drugs in the drug-loaded e-spun CA fiber mats and the corresponding as-cast CA films (cut into circular discs of ~2.8 cm in diameter) was quantified by dissolving the samples in 4 ml of dimethylsulfoxide (DMSO). After that, 0.5 ml of the solution was pipetted and added into 8 ml of the acetate buffer solution. Each drug-containing dilute solution sample was measured for the amount of the drugs using a Shimadzu UV-1601 UV-spectrophotometer at wavelengths of 274, 319, 232, and 327 nm for NAP, IND, IBU, and SUL, respectively. The amount of the drugs originally present in the samples was back-calculated from the obtained data against a predetermined calibration curve for each model drug. The presence of DMSO in the dilute solution had no obvious effect on the UV absorbance at the wavelengths investigated and the results were reported as averages from at least five measurements.

2.4.3. Drug-release assay

Total immersion method was used to study the release characteristics of the drugs from the drug-loaded e-spun CA fiber mats and the corresponding as-cast CA films. Both types of samples (cut into circular discs of ~2.8 cm in diameter) were immersed in 40 ml of the acetate buffer solution and incubated in a shaking water bath at the physiological temperature of 37 °C. At a specified immersion period ranging between 0 and 24 h (1440 min), 0.5 ml of the buffer solution was taken out. The amount of the drugs in the withdrawn solutions was determined using the UV-spectrophotometer at the same wavelengths previously mentioned against the predetermined calibration curve for each model drug. The calibration curve for each model drug was carried out in the concentration range of 0.0025–0.05 mg ml^{-1} in which a linear relationship between the UV absorbance and the drug concentration was realized. These data were carefully calculated to determine the cumulative amount of the drugs released from the samples at each specified immersion period. The experiments were carried out in triplicate. A statistical software SPSS version 12.0 was used to analyze the obtained data. The significance (P) for all the tests was set at $P < 0.05$. The release of the drugs from these samples was reported as the cumulative release of the drugs as a function of the immersion period.

3. Results and discussion

3.1. Morphology of neat and drug-loaded CA fiber mats

The as-prepared 16% w/v CA solution in 2:1 v/v acetone/DMAc was e-spun under an applied EFS of 12 kV/15 cm. A selected SEM image of the neat e-spun CA fibers is shown in Fig. 2(a). Clearly, only smooth fibers were obtained. The diameters of these fibers were 231 ± 17 nm. Due to the uniformity of the obtained fibers, the as-prepared CA solution was used as the base solution into which four different drugs were individually added (i.e., 20 wt.% based on the weight of CA powder). After complete dissolution of the model drugs, the resulting solutions were measured for their shear viscosity, conductivity, and surface tension, as summarized in Table 2. Evidently, the presence of the model drugs in the resulting solutions did not cause a significant change in the property values from those of the neat solution. These solutions were later e-spun and the selected SEM images of the drug-loaded e-spun CA fiber mats are shown in Fig. 2(b–e). Evidently, these drug-loaded fibers were smooth, with the average diameters of these fibers ranging between 263 and 297 nm. Additionally, since neither presence of the drug crystals nor other kinds of drug aggregates was observed on the surfaces of these fibers, it is postulated that the drugs were encapsulated well within the fibers. This is in contrast to the drug-loaded solvent-cast CA films which evidently showed the presence of either drug crystals or other kinds of drug aggregates on their surfaces (see Fig. 3).

The non-existence or the existence of the drug aggregates on the surface of the drug-loaded fibers or the drug-loaded films could also be due to the difference in the evaporation rate of the solvent during fabrication. The evaporation of the solvent from the fibers occurred in an extremely short time (i.e., during their flight to the collecting device). On the other hand, the evaporation of the solvent from the films occurred in a much longer time interval. The much longer time for evaporation of the solvent from the drug-loaded as-cast CA films could be responsible for the observation of the drug aggregates on these films.

3.2. Chemical integrity of drugs in drug-loaded CA fiber mats

Due to the application of a high electrical potential to the drug-containing CA solutions during e-spinning, it is questionable whether the chemical integrity of the drugs would be intact after such a treatment. To verify that, drug-loaded e-spun CA fiber mats were dissolved in DMSO-d_6 and the resulting drug-containing solutions were investigated by ^{1}H NMR. The solution from the neat e-spun CA fiber mat in DMSO-d_6 was used as an internal control. All the ^{1}H NMR spectra along with the chemical structure of the model drugs are illustrated in Fig. 4. The obtained results showed that the chemical integrity of all the model drugs was intact after the e-spinning process. ^{1}H NMR has also been used to verify the integrity of sodium salicylate (SS), diclofenac sodium (DS), NAP, and IND in the corresponding drug-loaded e-spun PVA fiber mats [10] and cefoxitin sodium after being released from a medicated poly(lactic-*co*-glycolide) (PLGA) fiber mat [26], while it was used as a means for estimating bovine serum albumin (BSA) loading in poly(ethylene glycol) (PEG)/polycaprolactone (PCL) core/shell nanofibrous scaffolds [27].

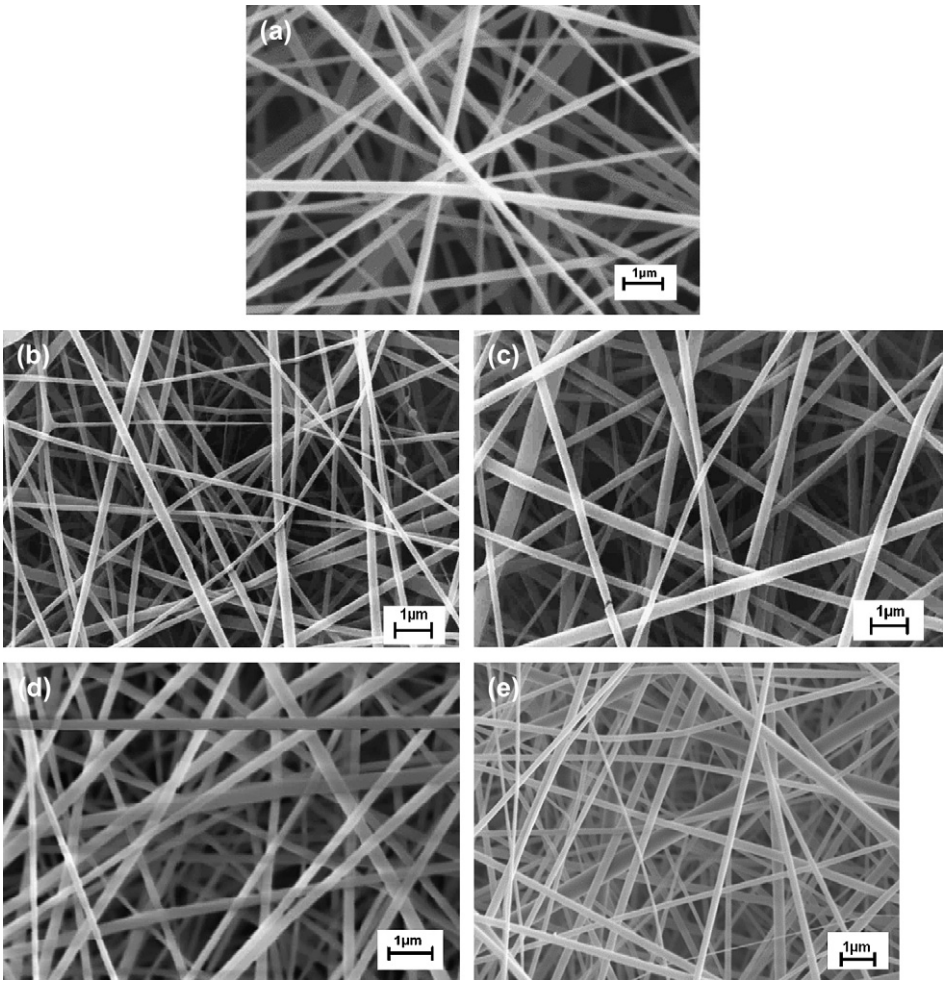

Fig. 2. Selected SEM images (magnification = 5000×; scale bar = 1 μm) of e-spun fibers from (a) neat 16% w/v CA solution in 2:1 v/v acetone:DMAc and the solutions containing (b) NAP, (c) IND, (d) IBU, and (e) SUL at a fixed amount of 20% by weight of CA. The electrostatic field strength was 12 kV/15 cm and the collection time was 10 min. The diameters of these fibers were 231 ± 17, 263 ± 19, 297 ± 14, 279 ± 11, and 286 ± 24 nm, respectively.

3.3. Thermal properties of neat and drug-loaded CA fiber mats

Some thermal properties of the model drugs and the neat and the drug-loaded e-spun CA fiber mats were investigated by DSC and TGA techniques. Fig. 5 shows DSC thermograms for the model drugs and the neat and the drug-loaded e-spun CA fiber mats. Within the temperature range investigated, all of the model drugs showed a single endothermic thermal transition, with the peak temperatures being observed at ~153, 160, 77, and 185 °C for NAP, IND, IBU, and SUL, respectively. These values corresponded to the melting transition of the model drugs (see Table 1). These peaks were absent or almost absent from the corresponding DSC thermograms for the drug-loaded e-spun CA fiber mats. Since neither presence of the drug crystals nor other kinds of drug aggregates was observed on the surfaces of these fibers and the chemical integrity of the drugs after e-spinning was intact, it is postulated that the absence of the melting peaks of the drugs was due to the inability of the drug molecules to form crystalline aggregates within the fibers. The most likely reason was the extremely rapid evaporation of the solvent from the fibers during e-spinning, as previously mentioned.

The neat e-spun CA fiber mat exhibited two endothermic thermal transitions, with the low-temperature endotherm (i.e., 50–110 °C) corresponding to the loss of moisture coupled with a glass transition, while the higher-temperature endotherm (i.e., 215–233 °C) corresponding to the melting range of the material (see Table 1). The glass transition temperature of CA was reported to occur over a wide temperature range [28], depending on the degree of acetyl substitution (DS) of the polymer, while the melting of CA (degree of

Table 2
Some properties of neat and drug-containing CA solutions

Type of CA solution	Viscosity (mPa s)	Conductivity (μS cm^{-1})	Surface tension (mN m^{-1})
Neat	419 ± 1.2	5.58 ± 0.05	35.2 ± 0.20
NAP-containing	431 ± 0.6	5.27 ± 0.13	32.8 ± 0.13
IND-containing	426 ± 0.8	5.34 ± 0.00	33.7 ± 0.28
IBU-containing	415 ± 1.5	5.16 ± 0.08	30.6 ± 0.34
SUL-containing	435 ± 1.0	6.18 ± 0.11	31.5 ± 0.08

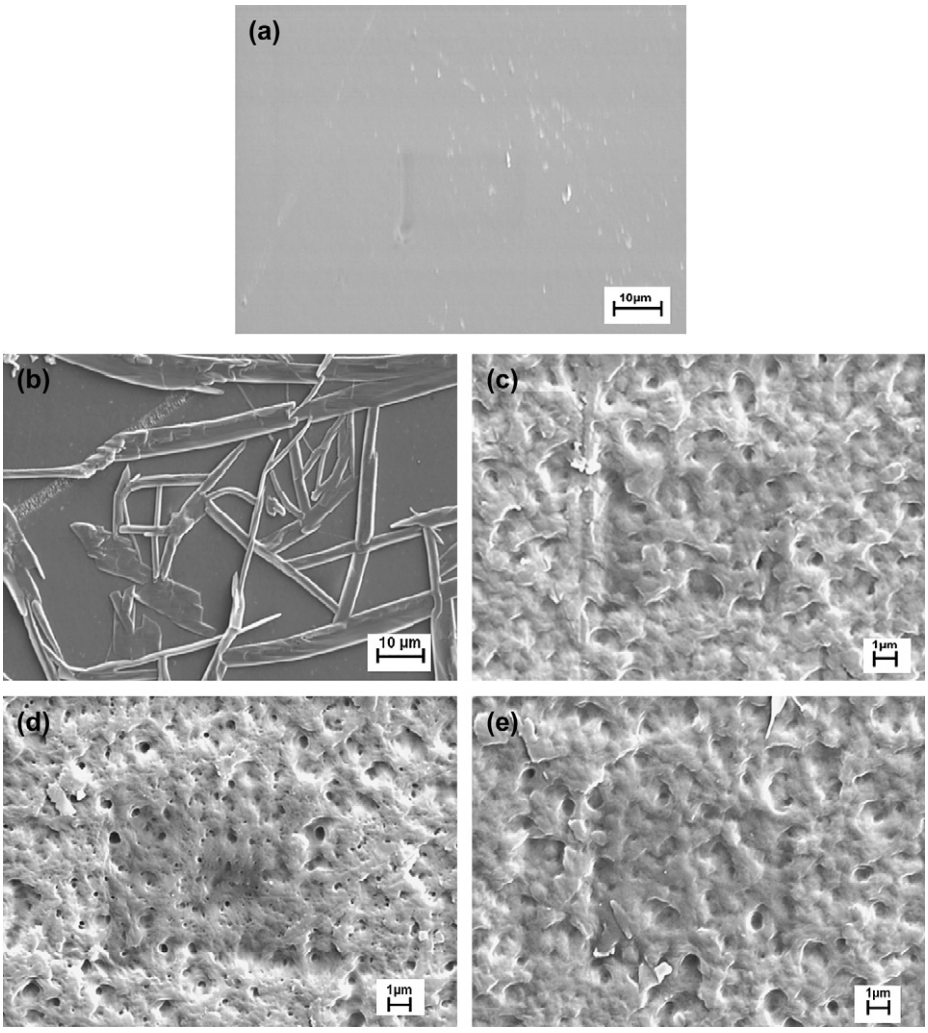

Fig. 3. Selected SEM images (magnification = 5000×; scale bar = 1 μm) of solvent-cast films from (a) neat 12% w/v CA solution in 2:1 v/v acetone:DMAc and the solutions containing (b) NAP, (c) IND, (d) IBU, and (e) SUL at a fixed amount of 20% by weight of CA.

polymerization ≈ 500–600; DS ≈ 2.4) in the form of solvent-cast film was reported to occur over a wide temperature range with the peak temperature being observed at ~224 °C [29]. All of the drug-loaded e-spun CA fiber mats also exhibited a loss of moisture coupled with a glass transition over about the same temperature range as that of the neat e-spun CA fiber mat, while their melting range was either disappeared or different from that of the neat e-spun CA fiber mat.

Fig. 6 shows TGA thermograms for the model drugs and the neat and the drug-loaded e-spun CA fiber mats. NAP, IND, and IBU exhibited one step in the loss of their mass, while SUL showed two such steps. Specifically, NAP showed the loss of its mass over the temperature range of 180–330 °C, IND over the temperature range of 220–380 °C, IBU over the temperature range of 145–245 °C, and SUL over the temperature ranges of 230–290 and 320–550 °C. Interestingly, only SUL had the char content of about 43% at 700 °C. The neat CA fiber mat exhibited two steps in the loss of its mass, with the first covering the temperature range of 35–120 °C corresponding to the loss of moisture (about 3%) and the second covering the temperature range of 250–410 °C corresponding to the thermal degradation of the material. The char content at 700 °C for the neat CA fiber mat was about 12%. Most of the drug-loaded e-spun CA fiber mats, except for IBU-loaded e-spun CA fiber mat, exhibited the loss of moisture over the temperature range of 35–120 °C and most of the drug-loaded e-spun CA fiber mats, except for SUL-loaded e-spun CA fiber mat, showed two more steps in the loss of their mass, obviously corresponding to the thermal degradation of the drugs and the CA matrix. SUL-loaded e-spun CA fiber mat was the only material that showed a greater char content than that of the neat CA fiber mat, confirming the presence of the drug within the material.

3.4. Swelling and weight loss of neat and drug-loaded CA fiber mats and/or films

The neat and the drug-loaded e-spun CA fiber mats were further characterized to determine their swelling behavior after submersion in the acetate buffer solution at 37 °C for 24 h (see Fig. 7). The degree of swelling of the neat e-spun CA fiber mat was 715%, while that of the neat e-spun CA fiber mats (the

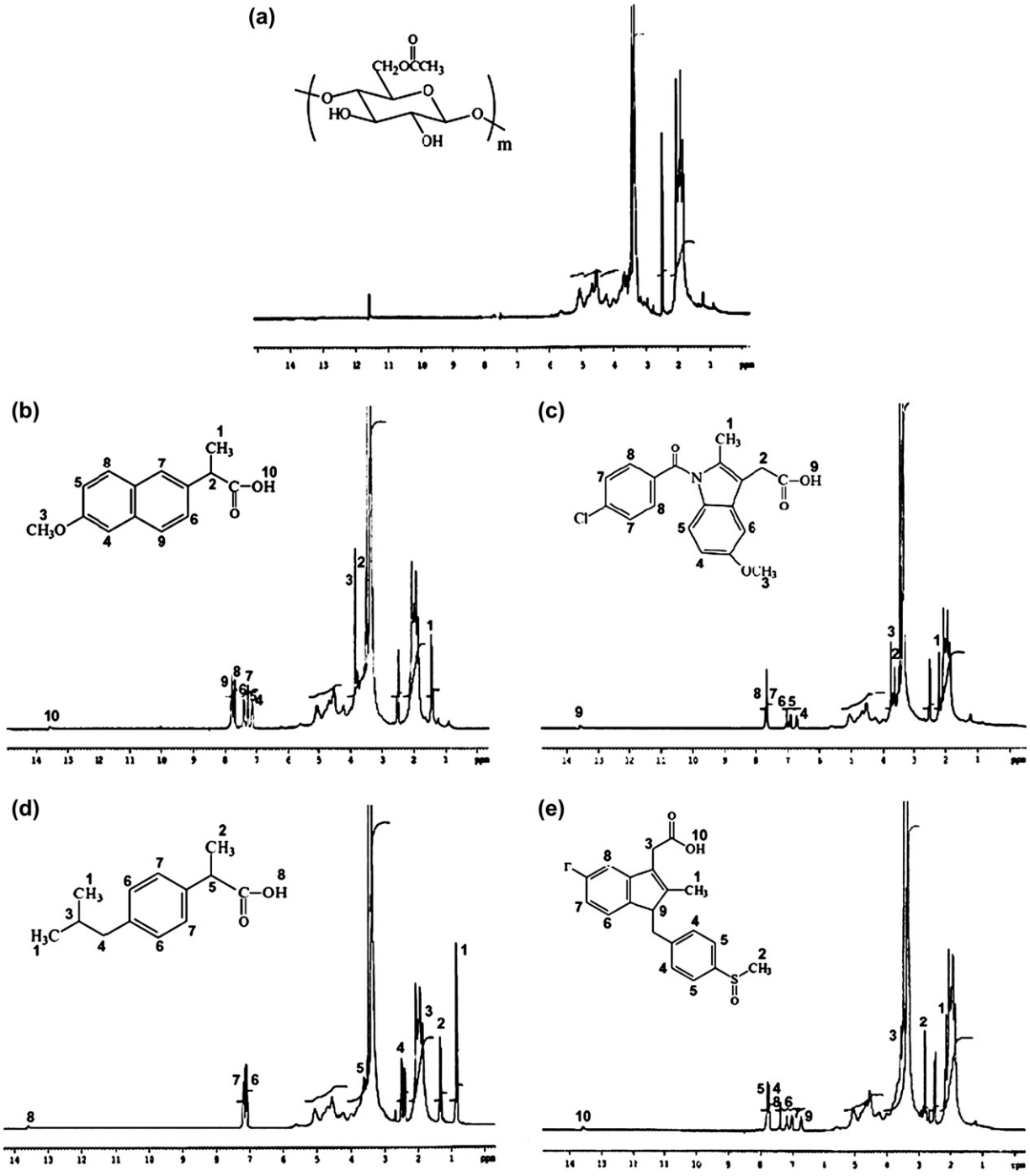

Fig. 4. ^{1}H nuclear magnetic resonance spectra of neat and drug-loaded electrospun CA fiber mats after being dissolved in DMSO-d_6: (a) neat, (b) NAP-, (c) IND-, (d) IBU-, and (e) SUL-loaded electrospun CA fiber mats.

average diameters of the individual fibers being in the range of 140–370 nm), after submersion in distilled water for 24 h, has recently been reported to range between 620 and 1110% [25], with the value for the neat e-spun CA fiber mat from 16% w/v CA solution in 2:1 v/v acetone/DMAc being 830% which is slightly greater than the value observed here. All of the drug-loaded e-spun CA fiber mats exhibited slightly lower values of swelling (i.e., 570–630%) when compared with that of the neat e-spun CA fiber mat. On the other hand, the corresponding solvent-cast films did not swell in the testing medium. Consequently, the large amount of water absorbed in the e-spun CA fiber mats, shown in Fig. 7, should attribute to the amount of water that is physically absorbed in the individual fibers and the amount of water that is retained by the capillary action in the inter-fibrous pores.

Fig. 8 shows weight loss of both the neat and the drug-loaded e-spun CA fiber mats and the corresponding solvent-cast films after submersion in the acetate buffer solution at 37 °C for 24 h. Evidently, the percentage of weight loss for the neat fiber mats and films was low (i.e., 1.1 and 0.6%,

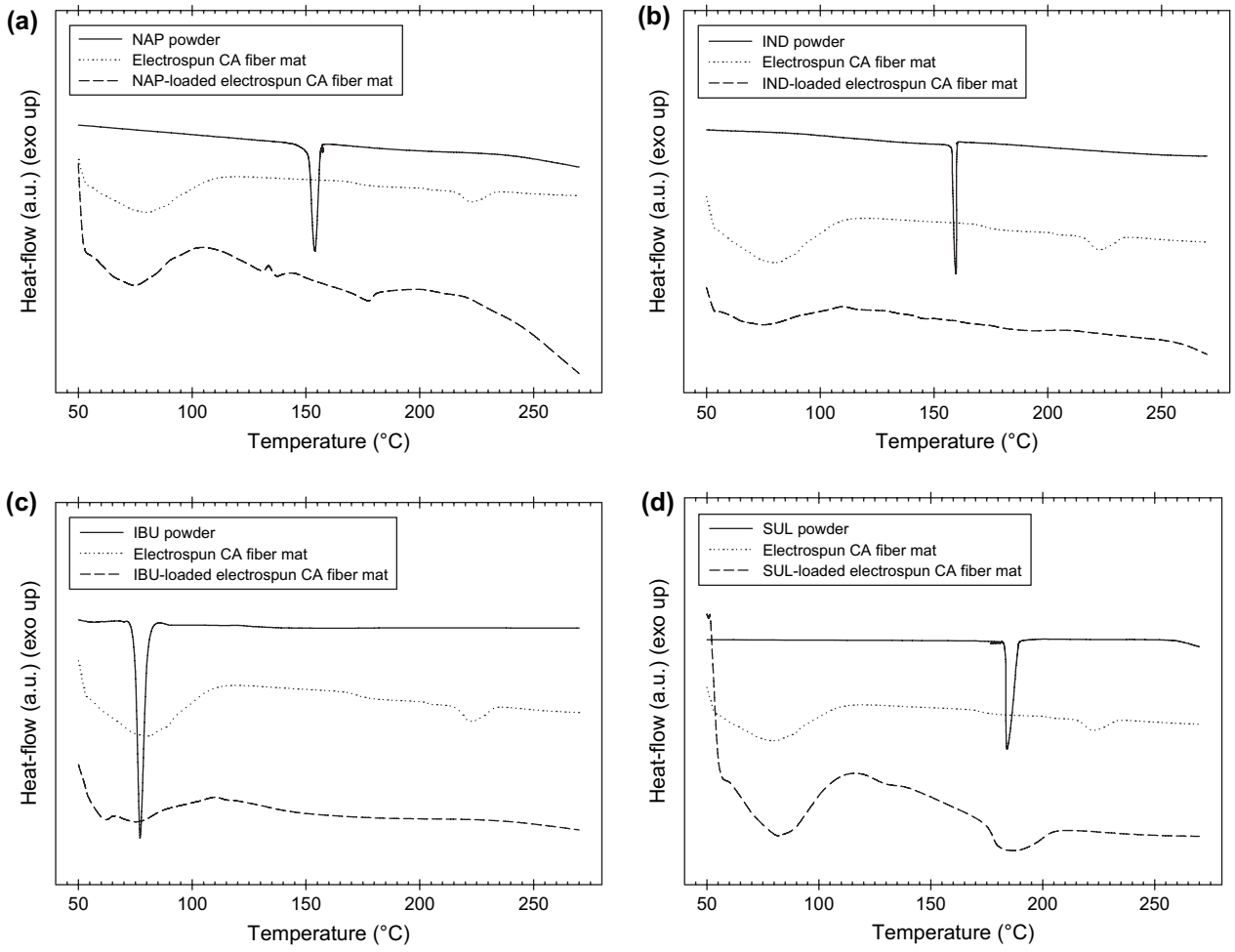

Fig. 5. Differential scanning calorimetric thermograms of neat electrospun CA fiber mat, pure model drugs of (a) NAP, (b) IND, (c) IBU, and (d) SUL, and corresponding drug-loaded electrospun CA fiber mats.

respectively). The percentage of weight loss for the neat e-spun CA fiber mats after submersion in distilled water for 24 h was in the range of 1.1–1.7% [25]. Since CA is soluble in glacial acetic acid [16], it should be partially soluble in the acetate buffer solution. However, due perhaps to the high crystallinity of the neat fiber mats (as inferred from the presence of the melting endotherm for the neat e-spun CA fiber mat; see Fig. 5) and films that limits the accessability of the buffer solution, the percentage of weight loss for both types of materials was then low.

On the contrary, due to the suppression of the crystallization of the CA matrix in the presence of the drugs (as inferred from the absence of the melting endotherm for the drug-loaded e-spun CA fiber mats; see Fig. 5), all of the drug-loaded fiber mats and films showed much greater weight loss than the neat materials. Generally, the fiber mat samples exhibited greater weight loss than the corresponding films, due possibly to the ability of the fiber mat samples to swell in the testing medium. Specifically, the percentage of weight loss for NAP-loaded e-spun CA fiber mat was the greatest at 18.8%, followed by those of IBU-, SUL-, and IND-loaded e-spun CA fiber mats at 13.7, 12.2, and 8.7%, respectively, while that for NAP-loaded as-cast CA film was the greatest at 15.0%, followed by those of IND-, SUL-, and IBU-loaded as-cast CA films at 9.3, 9.1, and 8.2%, respectively.

Though not shown, the physical integrity of the neat and the drug-loaded e-spun CA fiber mats was retained after submersion in the acetate buffer solution at 37 °C for 24 h.

3.5. Release of model drugs from drug-loaded CA fiber mats and films

Prior to investigating the release characteristics of the model drugs from both the drug-loaded e-spun CA fiber mats and the corresponding as-cast films, the actual amount of the model drugs within these samples needed to be determined. Table 3 summarizes the actual amount of the drugs present within these samples (reported as the percentage of the initial content of the drugs loaded in the spinning and the casting solutions, i.e., 20 wt.% based on the weight of CA powder). For the drug-loaded e-spun CA fiber mats, the actual amount of the drugs within these samples was in the range of 84–93%, while, for the drug-loaded as-cast CA films, it was in the range of 81–90%. The discrepancy from the ideal value of 100% for these samples could be due to the inhomogeneous distribution of the drugs in different areas of the fiber

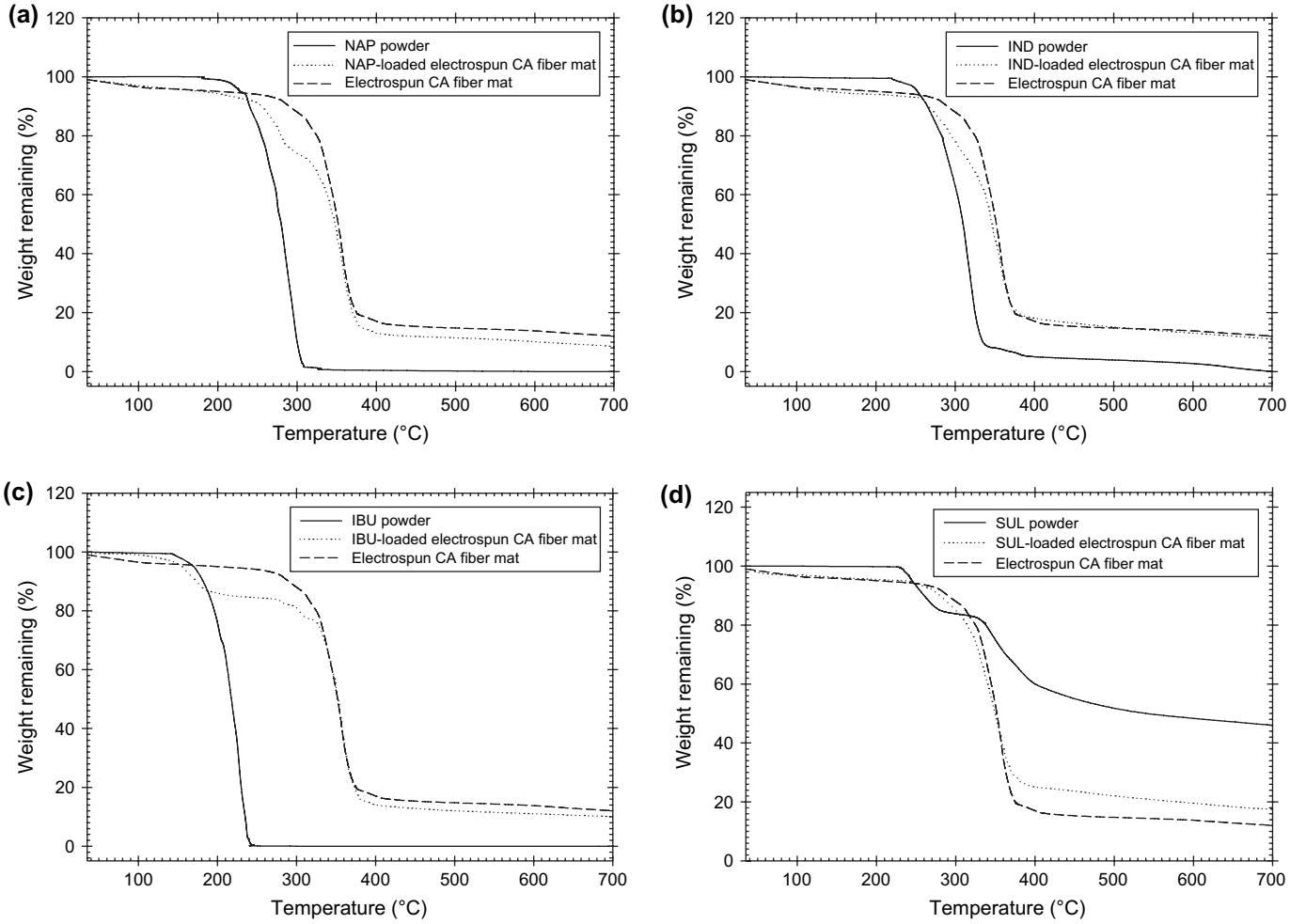

Fig. 6. Thermogravimetric analytical thermograms of neat electrospun CA fiber mat, pure model drugs of (a) NAP, (b) IND, (c) IBU, and (d) SUL, and corresponding drug-loaded electrospun CA fiber mats.

mats and films, which could be influenced by the fabrication techniques (e.g., the change in the local composition of the solutions during e-spinning and solvent-casting). These values were used as basis to arrive at the cumulative release of the drugs from these drug-loaded materials.

The release characteristics of the model drugs from the drug-loaded e-spun CA fiber mats and the corresponding as-cast films were carried out by the total immersion method, using the acetate buffer solution as the transferring medium, at the physiological temperature of 37 °C. The cumulative release of the drugs (reported as the percentage of the actual amount of the drugs present within the drug-loaded samples) as a function of immersion time from the drug-loaded fiber mat and the as-cast film samples is shown in Fig. 9. The results are shown in two ranges of the immersion time, i.e., 0–1440 and 0–120 min. At any given immersion time point, the release of the drugs from the drug-loaded e-spun CA fiber mats was greater than that from the corresponding as-cast films.

Evidently, NAP released from the NAP-loaded e-spun CA fiber mat showed a burst release during the first 60 min, leveled off between 60 and 300 min after immersion, and monotonously increased to reach the maximum value at 24 h (i.e., ~95%). The rapid release of NAP from the drug-loaded fiber mat was possibly due to the lack of interactions between the drug and the CA matrix and the high degree of swelling and the high solubility of the drug-loaded fiber mat in the testing medium (see Figs. 7 and 8). The release of IND, IBU, and SUL from

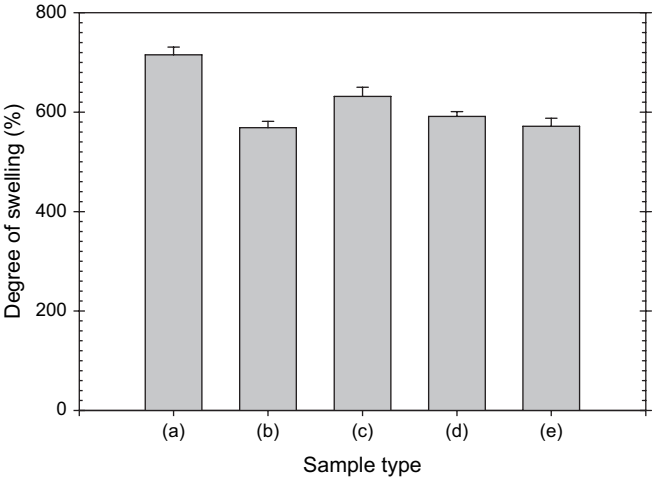

Fig. 7. Degree of swelling (%) of (a) neat, (b) NAP-, (c) IND-, (d) IBU-, and (e) SUL-loaded electrospun CA fiber mats.

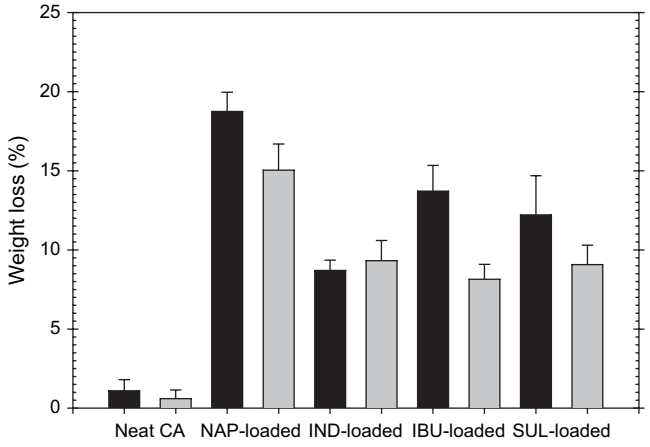

Fig. 8. Weight loss (%) of neat and drug-loaded electrospun CA fiber mats and corresponding solvent-cast films, respectively.

the corresponding drug-loaded e-spun CA fiber mats was relatively smoother (viz. without the obvious presence of the plateau region), with the maximum release of the drugs at 24 h being ~79, 81, and 78%, respectively. For the release of SS, DS, NAP, and IND from the drug-loaded e-spun PVA fiber mats, the total amount of the drugs released was a decreasing function of the molecular weight of the drugs [10]. Such results were not observed here, as the maximum release of the drugs from the drug-loaded fiber mats could be ranked as follows: NAP- > IBU- > IND- > SUL-loaded e-spun CA fiber mats, while the molar mass of the drugs could be ranked as follows: IBU < NAP < SUL ≈ IND (see Table 1).

All of the drug-loaded as-cast CA films showed a monotonous and gradual increase in the amount of the drugs released with increasing the immersion time. In comparison with the drug-loaded e-spun CA fiber mats, the drugs released from the drug-loaded film counterparts were much slower and the maximum amount of the drugs released was also much lower. Specifically, the maximum release of NAP, IND, IBU, and SUL from the drug-loaded films at 24 h was found to be ~54, 22, 39, and 19%, respectively. As a result, the maximum release of the drugs from the drug-loaded films could be ranked as follows: NAP- > IBU- > IND- > SUL-loaded as-cast films, which, obviously, is in the same order as that for the drug-loaded e-spun CA fiber mats. The much slower rates and the lower maximum amount of the drugs released from the drug-loaded films in comparison with those from the fiber mat counterparts could be due to the inability of the films to swell and to the lower weight loss in the testing medium (see Figs. 7 and 8) as well as to the much lower specific surface area (cf. SEM images in Figs. 2 and 3).

Table 3
Actual amount of model drugs within drug-loaded electrospun CA mats and as-cast CA films

Type of drug	Actual amount of drug based on the original amount of the drug-loaded (%)	
	Drug-loaded electrospun CA mats	Drug-loaded as-cast CA films
Naproxen	91.2 ± 1.68	90.3 ± 3.43
Indomethacin	87.6 ± 3.12	86.9 ± 4.18
Ibuprofen	93.3 ± 1.43	81.4 ± 3.11
Sulindac	83.5 ± 2.47	88.6 ± 2.78

The original amount of the model drugs loaded in the spinning and the casting solutions was 20% based on the weight of CA.

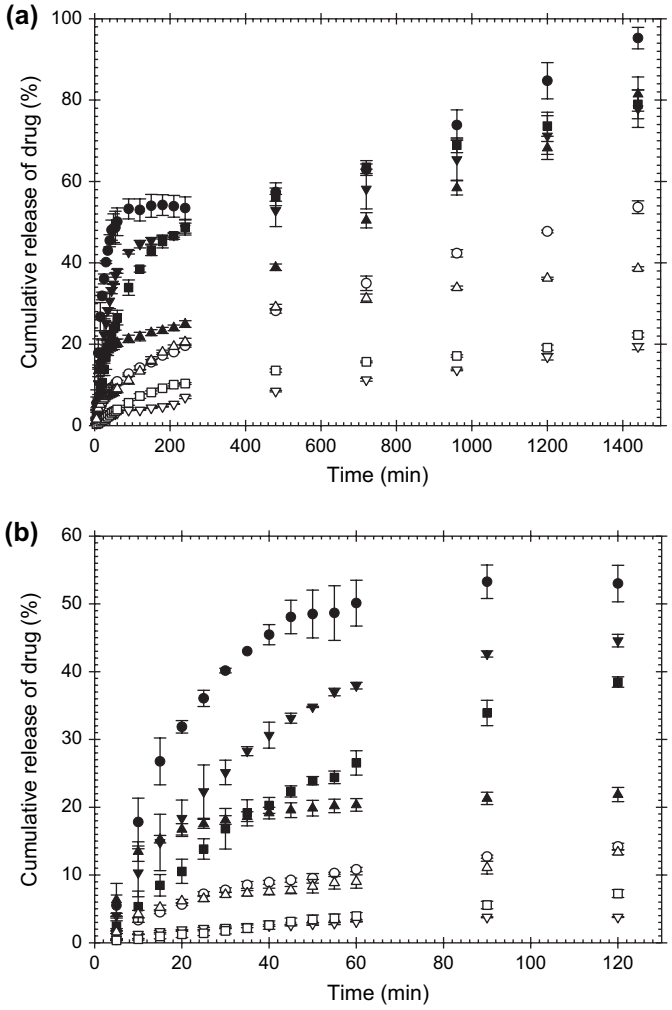

Fig. 9. Cumulative release profiles of model drugs from (●) NAP-, (■) IND-, (▲) IBU-, and (▼) SUL-loaded electrospun CA fiber mats and (○) NAP-, (□) IND-, (△) IBU-, and (▽) SUL-loaded solvent-cast CA films by total immersion technique during (a) 0–1440 min and (b) 0–120 min.

Prior to the drug release assay, all of the drug-loaded as-cast CA films exhibited some kinds of drug aggregates on their surfaces (see Fig. 3), but, after the drug release assay at 24 h, the surfaces of all of the drug-loaded films were as smooth as that of the neat one (i.e., Fig. 3a). This led us to believe that the release of the drugs from the drug-loaded films was due mainly to the gradual dissolution of the drug aggregates on the film surfaces, while the diffusion of the drugs incorporated within the films occurred in a much lesser extent. On the contrary, since no presence of the drug aggregates was found on the surface of the drug-loaded fibers (see Fig. 2), the release of the drugs from the drug-loaded fiber mats was mainly by the diffusion of the drugs from the fibers as the fiber mats could swell appreciably in the testing medium. While the fibrous morphology of the drug-loaded fiber mats after the

drug release assay at 24 h was still intact, the average diameter of the individual fibers of the mats was found to decrease slightly (results not shown).

The ability of a drug to release from a polymer matrix depends on many factors, e.g., the solubility of the drug in the polymer matrix, the solubility of the drug in the testing medium, the swelling ability and the solubility of the polymer matrix in the testing medium, the diffusion of the drug from the polymer matrix, etc. Among these, the swelling and the solubility of the polymer matrix in the testing medium and the solubility of the drug in the polymer matrix are the main contributing factors. According to Fig. 7, the swelling of all the drug-loaded e-spun CA fiber mats was inferior to that of the neat one and, among the various drug-loaded fiber mat samples, the one that contained IND showed the greatest swelling in the testing medium, while all others showed equivalent values. Based on the swelling studies, the ability for NAP to release from the NAP-loaded e-spun CA fiber mat should be the greatest, which is different from what was observed here. On the other hand, the results on the weight loss of both the drug-loaded fiber mats and films in the testing medium indicated that, for the drug-loaded fiber mats, NAP-loaded e-spun CA fiber mat should show the greatest release of NAP, followed by IBU-, SUL-, and IND-loaded ones, respectively, while for the drug-loaded films, NAP-loaded as-cast CA film should, again, show the greatest release of NAP, followed by the rest of the materials as they showed equivalent values.

The solubility of the drug in the polymer matrix is controlled by the solubility parameters of both the drug and the polymer matrix [30,31]. The solubility parameter (δ) relates directly to the cohesive energy density of a compound. Generally, the smaller the difference in the solubility parameters between the two components is, the greater their miscibility will be. The difference in the solubility parameters between a model drug and the polymer matrix is therefore a useful guide to determine the miscibility of the drug and the polymer matrix, and hence the ability of the drug to release from the polymer matrix. According to Table 1, the difference in the solubility parameters between CA [25.1 $(J\,cm^{-3})^{1/2}$] and SUL [24.8 $(J\,cm^{-3})^{1/2}$] was the smallest, followed by that between CA and IND [23.9 $(J\,cm^{-3})^{1/2}$], CA and NAP [21.0 $(J\,cm^{-3})^{1/2}$], and CA and IBU [19.1 $(J\,cm^{-3})^{1/2}$], respectively. Based on these values, the ability for the model drug to release from the CA matrix should fall in the following order: IBU > NAP > IND > SUL, which is slightly different from what was observed in this work.

4. Conclusions

Mats of ultra-fine cellulose acetate (CA; $M_w \approx 30\,000$ Da; degree of acetyl substitution ≈ 2.4) fibers containing four different types of model drugs, i.e., naproxen (NAP), indomethacin (IND), ibuprofen (IBU), and sulindac (SUL), were successfully prepared by electrospinning from 16% w/v CA solutions in 2:1 v/v acetone/*N*,*N*-dimethylacetamide (DMAc). The amount of the drugs in the solutions was fixed at 20 wt.% based on the weight of CA powder. These drugs are used in the symptomatic management of painful and inflammatory conditions. The morphology of the drug-loaded electrospun (e-spun) CA fiber mats was smooth, with the average diameters of these fibers ranging between 263 and 297 nm. No presence of the drug aggregates of any kind was observed on the surfaces of these fibers, suggesting that the drugs were encapsulated well within the fibers. On the contrary, the corresponding drug-loaded solvent-cast CA films showed evidence of drug aggregates on their surfaces.

All of the drug-loaded e-spun CA fiber mats swelled very well after submersion in the acetate buffer solution at 37 °C for 24 h (i.e., 570–630%), while the corresponding film counterparts did not swell at all in the same medium. While the percentage of weight loss for the neat fiber mats and films was low (i.e., 1.1 and 0.6%, respectively), that for the drug-loaded fiber mat and film samples was much greater (ranging from 8.7 to 18.8% for drug-loaded fiber mats and from 8.2 to 15.0% for drug-loaded films). The actual amount of the model drugs in the drug-loaded fiber mat and film samples was determined to range between about 84 and 93% for the drug-loaded fiber mats and between about 81 and 90% for the drug-loaded films. Finally, the release characteristics of the model drugs from these samples were carried out by the total immersion method in the acetate buffer solution at 37 °C. At any given immersion time point, the amount of the drugs released from the drug-loaded e-spun CA fiber mats was greater than that from the corresponding as-cast films. The maximum release of the drugs from both the drug-loaded fiber mats and films was found in the following order: NAP > IBU > IND > SUL.

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