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Physicomechanical properties and in vitro release behaviors of electrospun ibuprofen-loaded blend PEO/EC fibers

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Abstract

Electrospinning is a fiber manufacturing technique with the possibility of encapsulating high levels of small molecule drugs while providing controlled release rates. In this study, electrospun blend fibers were produced from polyethylene oxide (PEO) and ethyl cellulose (EC) at various compositions to encapsulate a poorly water-soluble drug of ibuprofen (IBP) at 30% loading. Microscopic evaluation showed smooth and defect-free fiber morphologies for blank and IBP-loaded PEO/EC fibers. The average fiber diameters and fiber yields suggested a potential optimization on the blend fiber composition for the electrospun drug-eluting PEO/EC fibers, where the highest average fiber diameter and fiber yield occurred at 50PEO/50EC fiber composition. Surface wettability studies demonstrated the effects on surface hydrophobicity from blend fibers of water-soluble PEO and hydrophobic EC as well as the incorporation of IBP. In addition, blend fibers containing more PEO promoted the water absorption rates through dissolution of the polymer matrix. Furthermore, results from mechanical testing of the blend fibers showed the highest fiber elastic modulus and tensile strength at fiber compositions in between 75PEO/25EC and 50PEO/50EC, corresponding to the average fiber diameter measurements. The in vitro IBP release rates demonstrated a dependence on the EC compositions supported by the surface wettability and water absorption rate studies. In general, our work demonstrated the ability to electrospin blank and IBP-loaded PEO/EC fibers with the scientific understandings of EC compositions on modulations of fiber physicomechanical properties and in vitro drug release rates. The findings from the work indicated the potential engineering and pharmaceutical applications of electrospun drug-eluting fibers for topical drug delivery.

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Shih-Feng Chou: Conceptualization, Methodology, Formal analysis, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Billie Cheyenne Hawkins:** Validation, Investigation, Writing – original draft. **Eric Burnett:** Validation, Investigation, Writing – original draft.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Keywords

Electrospun blend fiber; Ethyl cellulose; Fiber yield; Mechanical properties; Surface contact angle; Drug release

1. Introduction

Nanofibers have attracted many applications in electrically conductive nanocomposites for electromagnetic interference shielding effectiveness [1–3]. Among many available fiber-manufacturing techniques, electrospinning appears to be the ideal candidate for the production of polymer nanofibers. During electrospinning, polymer fibers are produced by charging and stretching of a viscous polymer solution using an electric field, and the resulting fibers have a fiber diameter ranging from several tenths of nanometers to a few micrometers in diameter. Unlike traditional polymer microfibers drawn or extruded from polymer melts or solutions, electrospun fibers have a much larger surface area to volume ratio than those of the traditional fibers [4]. This unique physical property provides a more surface specific interaction in biomedical applications, including fibrous membranes in wound dressings, tissue regeneration scaffolds, and implanted devices such as drug-eluting stents [5].

Electrospun fibers are capable of carrying and/or encapsulating a wide variety of biological and chemical agents up to 60% of loading [6]. In particular, electrospinning provides a direct method to incorporate poorly water-soluble drugs with improved bioavailability and the ability to achieve controlled release behaviors [7]. Depending on the route of administration, drug delivery from electrospun drug-eluting fibers typically consists of one or more of the mechanisms in surface wetting, drug dissolution from the polymer matrix, and drug diffusion from the swelled polymer fibers [8]. In this regard, strategies in modulating drug release rates can be achieved by adjusting the physicochemical properties of the polymer used in electrospinning. For example, electrospun drug-incorporated blend fibers from water-soluble polyvinylpyrrolidone and hydrophobic hydroxypropyl methylcellulose acetate succinate at various compositions provided tunable release rates through levels of fiber surface wettability that led to a combination of drug dissolution and diffusion processes during the in vitro drug release studies [9]. Others blended cellulose acetates and ethyl cellulose at various compositions to achieve sustained drug release behaviors [10].

In the attempt to produce cellulose-based wound dressings, hydrophobic ethyl cellulose (EC) is an ideal candidate for electrospun drug-eluting fibers due to its nontoxicity, biocompatibility, and excellent mechanical properties [11]. EC has been widely used in pharmaceutical coatings of solid dosage drugs for taste-masking ability while providing sustained release behavior through pH dependency [12]. EC has gained attention as a fiber mesh in drug delivery system in recent years and shown potential as a topical drug delivery vehicle [13]. EC fibers retain their mechanical properties upon contact with physiological solution allowing the fiber meshes to serve as a comparable tissue scaffold in wound healing applications. Drug release from an EC fiber mesh system occurs upon contact with release media where the drug dissolves and diffuses through the cellulose system pores into the

release media [12]. Employment of hydrophobic EC to accomplish a rapid and burst release behavior is an obstacle due to their poor solubility in physiological solution. In multiple research EC has been shown to exhibit swelling in the presence of gastric juice, making it permeable for water and permitting extended modified drug release [14–18].

Polymers such as EC are better suited to provide a sustained release profile for an extended period as compared to water-soluble polymers [19]. Therefore, the incorporation of a water-soluble copolymer is desirable to combat EC's remarkable hydrophobicity. The water-soluble polymer polyethylene oxide (PEO) has been routinely used in biomedical applications due to its nontoxicity, intrinsic solubility, biocompatibility, and good mechanical properties. Drug release from a PEO fiber mesh system occurs upon contact with a release media where the drug is extricated through polymer matrix dissolution [20]. PEO has also been utilized to aid in emulsion of lipids as well as other non-polar substances. Furthermore, PEO is unreactive toward proteins and cells (e.g., suppressing adhesion of the biological macromolecules) and a nonthrombogenic material, providing its biocompatibility in biomedical applications [21].

In this study, we electrospun PEO/EC blend fibers at various compositions and characterized their corresponding physicomechanical properties. A poorly water-soluble drug, ibuprofen (IBP), was used as the model drug in the PEO/EC fibers to study the in vitro drug release behaviors. Our hypothesis is that fiber physicomechanical properties are determined by the composition of PEO/EC fibers while the in vitro drug release rates depend on fiber wettability and water absorption rates. Results suggested that average fiber diameters and average fiber yields approached to a maximum at 50PEO/50EC fiber composition. In addition, increasing PEO contents in the PEO/EC fibers promoted the surface wettability of the fibers and their water absorption abilities. More importantly, mechanical properties of the PEO/EC fibers suggested a potential optimized fiber composition for high modulus and strength application, perhaps associated with the average fiber diameter. The in vitro release rates of IBP from PEO/EC fibers showed a dependency on fiber composition, where fast release was related to dissolution of the PEO matrix and slow release was based on drug diffusion from the EC phase of the blend fibers. In general, our work provides scientific understandings on the physicomechanical properties and drug release behaviors of the electrospun PEO/EC blend fibers. The drug-eluting PEO/EC fibers have the potential engineering applications in tunable drug release carriers.

2. Material and methods

2.1. Materials

Polyethylene oxide (PEO) with an average molecular weight (Mw) of approximately 900 kDa (POLYOXTM™ 1105), and ethyl cellulose (EC) with an average nominal viscosity of 20 (ETHOCEL™ Standard 20) were kindly provided by DuPont de Nemours, Inc. (Wilmington, DE, USA). Ibuprofen (IBP) (2-(4-isobutylphenyl)propanoic acid, 98% purity) was purchased from Ark Pharm Inc. (Arlington Height, IL, USA). Chloroform (> 99.8% stabilized ACS), phosphate-buffered saline (PBS) tablets (Biotechnology Grade), and 95% ethanol (denatured ACS) were purchased from Avantor (Radnor, PA, USA). All other chemicals were of reagent grade and used as received without further purification.

2.2. Polymer solution preparation

5% (w/v) PEO and 20% (w/v) EC solutions were prepared by dissolving appropriate amount of the polymer powders in chloroform. In short, masses of polymer powders were measured using a Mettler Toledo AG245 analytical balance (Columbus, OH, USA), whereas the corresponding volumetric amounts of chloroform were dispensed into glass vials using a micropipette (resolution = 0.5 μL). Glass vials containing PEO/EC in chloroform were placed on a Thermo Scientific™ Labquake™ rotisserie mixer (Waltham, MA, USA) for dissolution at room temperature. To prepare IBP-loaded PEO/EC solutions, the actual masses of polymers used for each solution were considered in order to calculate the appropriate amounts of IBP 30% (w/w) for various blends of PEO/EC solutions. IBP was introduced to the polymer solutions with continuous rotating mixing for at least an hour prior to electrospinning.

2.3. Fiber electrospinning

Electrospinning was conducted within 48 hrs of solution preparation after complete dissolution of polymers and drugs in the solvent. The prepared polymer solution was loaded into a 3-mL BD Luer-lock™ disposable syringe (Franklin Lakes, NJ, USA) that was attached to a 21-G blunt needle. The needle/syringe assembly was then placed onto a NE-1000 programmable single syringe pump (Farmingdale, NY, USA). Calibration of the syringe pump was performed regularly to a diameter of 8.725 mm for the 3-mL BD syringe to dispense polymer solution at a flow rate of 20 μL/min. During electrospinning, a total of 2 mL of the polymer solution, recorded by the programmable pump, was dispensed under an applied voltage of 10 kV by a Gamma High Voltage DC power supply (Ormond Beach, FL, USA) attached to the blunt needle. Fibers were collected on a grounded stationary collector plate that was covered in a layer of wax paper in a chemical fume hood with temperatures and humidity ranged from 20° to 21°C and 35–45% RH, respectively. The deposition distance of the fibers, distance between the tip of the needle and the collector plate, was maintained at 12 cm. After electrospinning, fiber samples were stored in protective envelopes using additional wax paper prior to characterizations.

2.4. Fiber morphology fiber diameter measurements

The morphologies of the electrospun blank and/or IBP-loaded PEO/EC fibers were evaluated by a scanning electron microscope (SEM). Circular disc punches obtained from the fiber meshes were placed on a SEM sample holder using carbon tapes. SEM micrographs were acquired using a Hitachi TM4000Plus system (Tokyo, Japan) at 15 kV with a working distance of approximately 5.5–6.0 mm.

2.5. Fiber diameter and fiber yield measurements

Average fiber diameters were measured using the ImageJ software, National Institutes of Health (Bethesda, MD, USA), on the collected SEM images. Specifically, 30 random measurements were taken from three separate SEM micrographs to determine the average fibers diameter and the standard deviations of each sample (n = 30).

Average fiber yields were determined by calculating the area density of the fiber mats. Briefly, 7/16″ diameter circular discs were taken from the electrospun fiber meshes at

locations near the center of the deposition area. The mass of each disc was measured using a Metter Toledo AG245 (Columbus, OH, USA) analytical balance. Results were averaged on three independent measurements (n = 3).

2.6. Water contact angle studies

The surface wettability of blank and IBP-loaded PEO/EC fibers at various compositions was quantified by water contact angle measurements. In brief, a single droplet of 4-μL PBS solution was placed on the surface of the fiber mesh, and videos of the events were recorded from each fiber sample. Picture frames of the initial contact angles, defined as early as the droplet was placed onto the surface of the fiber meshes, for each sample were withdrawn from the video clips and measured by the ImageJ software, National Institutes of Health (Bethesda, MD, USA). Results were averaged on three independent measurements (n = 3).

For measurements of the water absorption rates, picture frames at various time points (up to 60 s) were taken from the video recordings that captured the placement and absorption events of the 4-μL PBS droplet for the blank and IBP-loaded PEO/EC fiber discs. The average contact angles at various time points were measured using the same method as described above. The change on the contact angle (°/s) over time through linear curve fitting was defined as the water absorption rate. Results were averaged on three independent measurements (n = 3).

2.7. Mechanical testing

Dog-bone tensile specimens were punched from each of the blank and IBP-loaded PEO/EC fiber mats using an ODC stainless steel die (Waterloo, ON, Canada) according to ASTM standard D1708–18 [22]. The dimension of the dog bone specimen had a nominal length of 22 mm and a nominal width of 5 mm. The thickness of each sample at the nominal region was measured by the digital thickness gauge for engineering stress and engineering strain calculations.

Uniaxial tensile tests were performed on a single column screwdriven Instron® 3342 universal materials testing machine (Norwood, MA, USA), equipped with a 10 kN load cell, under 24 ± 1 °C and 45 ± 5% RH in accordance with ASTM standard D882–18 [23]. The applied strain rate was 0.01/s. Load and displacement data was recorded from the instrument for calculation of the stress-strain curve of each sample. Young's modulus, tensile strength, and percent elongation to failure were determined from the corresponding stress-strain curve of each sample in Microsoft Excel (Redmond, WA, USA) (n = 3).

2.8. In vitro drug release studies

7/16″ diameter circular disks were taken from each electrospun IBP-loaded PEO/EC fiber mesh using a metal die. Masses of the cut fiber samples were measured by a Metter Toledo AG245 (Columbus, OH, USA) analytical balance. Based upon mass of each disc and due to the limited solubility of the IBP in PBS (i.e., LogP = 3.5 [24,25]), 1–3 mL of PBS (pH ~7.3) and 95% ethanol mixtures (50/50) were prepared as the release media. The release media were deposited into glass vials and pre-warmed to 37 °C in a Thermo Scientific™ MaxQ

4450 (Waltham, MA, USA) orbital shaker at 120 rpm. IBP-loaded fiber samples were then placed in the incubator shaker for in vitro release of IBU.

A 40-μL sample of the release media, containing unknown concentration of the IBP, was removed from the corresponding vial and placed in a 1.5-mL microcentrifuge tube at predetermined time points of 10, 20, 30, 60, and 120 min using a separate and clean pipette tip for every extraction. A 40-μL of the fresh PBS/ethanol (50/50) release media was pipetted into each vial to replace the volume taken at each collection time to ensure consistent volume of the total release media during the assay. Before and between each sample collection, the release media release vials were placed in the incubator to maintain the proper temperature.

Standard solutions of IBP at concentrations of 400, 200, 100, 50, and 25 ppm were prepared using serial dilation methods. Liquid specimens of the standard and unknown IBP samples collected at various time points were analyzed using a Thermo Scientific NanoDrop™ 1000 UVVis spectrophotometer (Waltham, MA, USA) at 265 nm. Sample background was calibrated using the PBS/ethanol (50/50) solution. Standard solutions of IBP and unknown concentrations of IBP samples were then placed onto the pedestals for measurements with cleaning procedures in between samples to prevent carryovers from previous specimens. Cleaning and calibration procedures were frequently repeated after every 10 measurements. The resulting intensities of IBP at 265 nm from the unknown samples were compared to the standard IBP curves to determine the in vitro release rates of the collected liquid samples at each time point. Results were averaged on three independent measurements (n = 3).

2.9. Statistical analyses

Results were expressed as average ± standard deviation (SD). Statistical studies of the averages were performed using GraphPad Prism (San Diego, CA, USA) on one-way analysis of variance (ANOVA). Significance was accepted with $P < 0.05$.

3. Results and discussion

3.1. Polymer solution preparation and electrospinning

The initial observations on the solution behaviors after blending 5% (w/v) of PEO and 20% (w/v) of EC in chloroform showed the miscibility of both polymers in the solvent. After thorough mixing, clear and transparent solutions without residuals were obtained at various PEO/EC compositions with viscosities suitable for electrospinning. During electrospinning, various blank PEO/EC solutions produced continuous fibers with visual confirmations of Taylor cones and fiber whipping behaviors. Studies showed that PEO fibers were able to electrospin into fibers without beads at 3 wt% in chloroform [26]. Others electrospun EC fibers using ethanol as a solvent and demonstrated a fiber morphological change from beads to uniform fibers from 17 to 25 wt% solutions [27]. These published results suggested the polymer concentrations for the electrospun blend PEO/EC fibers in this work.

To electrospin drug-eluting fibers, the blank PEO/EC solutions at various volumetric concentrations were loaded with 30% (w/w) IBP. In all compositions, IBP powders were readily dissolved in PEO/EC solutions within 45 min, resulting in a clear and viscous

solution. These experimental observations showed the capability of loading a high content of poorly water-soluble drug, such as IBP, in blend PEO/EC polymer solutions without reaching solubility limits as well as phase separation.

3.2. Fiber morphology observations

Following electrospinning, disc samples of blank PEO/EC and IBP-loaded PEO/EC fibers at various compositions were prepared for SEM imaging on their corresponding fiber morphologies and microstructures. Fig. 1 shows the SEM images of various compositions of electrospun blank and IBP-loaded PEO/EC fibers. According to the SEM observations, the blank PEO/EC fibers at various compositions exhibited smooth fiber surfaces and consistent fiber mat porous structures without flaws and defects. After loading the PEO/EC fiber with 30% (w/w) IBP, the drug-eluting fibers showed no indication of drug re-crystallization after electrospinning, suggesting the compatibility of the solvent to the polymer/drug systems. Nonetheless, both blank and IBP-loaded 100PEO/0EC fibers displayed a small amount of beading, potentially due to the low concentration of the polymer solution for electrospinning. These SEM observations indicated the potential use of electrospun PEO/EC fibers as a drug delivery platform with the ability to encapsulate a poorly water-soluble drug, such as IBP, at a high loading (i.e., 30% w/w).

3.3. Fiber diameter measurements

SEM images of the electrospun blank and IBP-loaded PEO/EC fibers were analyzed by the ImageJ software to obtain the average fiber diameter, and the results are shown in Fig. 2. The average fiber diameters of the blank PEO/EC fibers increased with increasing EC contents with a maximum of average fiber diameter of 2.94 ± 0.36 μm at 50PEO/50EC composition. This observation was associated with the increase of total polymer contents in the blend PEO/EC solutions as the weight contents of the PEO and EC were 5% and 20%, respectively. In addition, the incorporation of the IBP in PEO/EC blend fibers appeared to have minimal effects to the average fiber diameter as the data suggested a similar trend to the blank fibers. The average fiber diameters exhibited a maximum of 3.10 ± 0.40 μm at 50PEO/50EC compositions after incorporation of the IBP.

Studies showed that the average fiber diameters of 15% (w/v) electrospun EC fibers in various THF/DMAc solvent ratios peaked at approximately 1.1 μm [28]. The average fiber diameter of our pure EC fiber exhibited an average fiber diameter of 1.57 ± 0.26 μm, which is within the range of the reported value, considering our polymer solutions contained 20% (w/v) EC. In another study, water soluble polyvinylpyrrolidone (PVP) was incorporated with 20% (w/w) IBP for electrospinning [29]. Results showed an average fiber diameter of 0.74 ± 0.13 μm for the IBP-loaded PVP fibers with smooth fiber surfaces and no beads formation, indicating the ability of the polymer matrix as a spatial barrier to promote solid dispersions of poorly water-soluble drugs and reduce drug recrystallization within the drug-polymer composites. Our findings of the IBP-loaded PEO/EC fibers exhibited a similar behavior, demonstrating the compatibility of the blend PEO/EC polymer systems with a poorly water-soluble drug at high loading.

In both blank and IBP-loaded PEO/EC fibers, increasing EC contents yielded larger fiber diameters with a more uniform fiber structure due to the increase of the solid contents of the blend polymer system. Studies suggested an increase of average fiber diameter of the electrospun fibers with increasing molecular weight of the polymer solution [30,31]. In particular, the average fiber diameter peaked at approximately 50% EC content by volume. This result suggested a potential optimized PEO/EC composition for largest average fiber diameter due to each polymer's unique properties that contributed to the blend fibers following rule of mixtures. In a study, blend chitosan and polylactide solutions were prepared in trifluoroacetic acid at various blend ratios for electrospinning [32]. Results showed that the ratios of chitosan and polylactide in the polymer blends played an important role to the statistical distributions of the average fiber diameters. The electrospinnability of the blend solutions and their corresponding fiber diameters were attributed to the degree of polymer chain entanglement in the blend solutions at various compositions. In general, our results showed the average fiber diameter peaked at 50% EC content in the electrospun blank and IBP-loaded PEO/EC fibers.

3.4. Fiber yield measurements

Fiber yields were determined for blank and IBP-loaded PEO/EC fibers at various compositions using area density measurements, and the results are shown in Fig. 3. For the blank PEO/EC fibers, results suggested little variations on the fiber yields irrespective of the EC contents in the blend fibers. The average fiber yields of the blank PEO/EC fibers ranged from 0.56 ± 0.16 mg/cm^2·h to 1.03 ± 0.07 mg/cm^2·h. Since the throughput rates of the polymer solutions at the pump were fixed at 20 μL/min for all blank PEO/EC compositions, the fiber production rates were expected to have minimal changes, depending on the overall polymer concentration (i.e., wt%) of the PEO/EC solutions.

In contrast, the IBP-loaded PEO/EC fibers illustrated a more prominent variation of the average fiber yields at various EC contents in the blend fibers, using the same throughput rates of 20 μL/min at the pump. The average fiber yields of the IBP-loaded PEO/EC fibers exhibited a maximum fiber yield of 4.88 ± 0.06 mg/cm^2·h for 50PEO/50EC compositions. Other blend compositions of IBP-loaded PEO/EC fibers showed a higher average fiber yield as compared to the blank counterparts, suggesting the improvement of "whipping" effect during electrospinning after incorporation of the IBP in PEO/EC solutions. This result demonstrated the role of small molecule drugs on the improvement of chain entanglements in electrospun fibers that promoted the electrospinnability of PEO/EC fibers, resulting in an increase of average fiber yields after electrospinning.

Electrospun blend PEG/PEO fibers were produced using targets of standard and sharpened electrodes, and the average relative yields were approximately 2 mg and 8 mg for the corresponding electrodes, respectively [33]. According to the study, the blend solutions contained approximately 50% of the polymers and were electrospun for 120 μL, leading to a theoretical fiber yield of 60 mg if all fibers were collected in between the electrodes. The relative low fiber yields for the two electrodes might be due to the specific fiber harvesting method as well as measurement methods of the fiber mass, which was only in between the electrodes. In another study, a circular cylinder was used as an emitting electrode for

tip-less electrospinning of PEO solutions [34]. Results of the collected fiber mats showed an increase of fiber production rates from 0.11 to 0.15 g/cm^2·h as the applied voltage increased from 60 to 80 kV. Others used a coaxial cylindrical setup in the vertical configuration (to the axial) to electrospin nylon-6 solution from the outer surface of the core electrode to inner surface of the shell electrode to achieve a fiber production rate greater than 5 g/h [35]. These fiber production rates were much greater than the single jet setup, where the fiber mass production rate was typically 0.1–1.0 g/h, which was limited by the throughput rate of the pump [36].

3.5. Surface wettability studies

In this study, PEO/EC fibers were electrospun as a platform for topical drug delivery applications based on our previous work in modulating drug release rates through drug-polymer interactions [37]. EC is a hydrophobic polymer, and electrospun EC fiber mats exhibit micro- to nano-sized porous architectures that impede the wettability of the fiber mat surfaces due to the surface tension of physiological fluids. In contrast, PEO is a water-soluble polymer that will attract and absorb physiological fluids upon contact. Therefore, blending PEO and EC at various compositions for electrospinning allows the fibers to exhibit levels of surface wettability and water absorption rates, which may provide an alternative strategy in modulating drug release rates.

The surface wettability studies on electrospun blank and IBP-loaded PEO/EC fibers were performed using water contact angle measurements at room temperature. The images of the water droplets on representative blank PEO/EC fibers discs are shown in Fig. 4(a), whereas the results of the average water contact angles for blank and IBP-loaded PEO/EC fibers at various compositions are shown in Fig. 4(b). Increasing EC contents in the PEO/EC fibers increased the average water contact angles for blank and IBP-loaded PEO/EC fibers. In particular, the average contact angles increased from 103.6 ± 1.3° to 110.4 ± 1.7° for blank PEO/EC fibers with increasing EC concentrations. Similarly, the average contact angles increased from 97.1 ± 4.2° to 116.7 ± 2.7° for IBP-loaded PEO/EC fibers with increasing EC concentrations. Notably, using linear approach to curve-fit the average contact angles data, the IBP-loaded PEO/EC fibers exhibited a 3-fold greater slope than the blank PEO/EC fibers. This finding suggested the role of hydrophobic IBP (i.e., LogP = 3.5) in PEO/EC fibers that further promoted the non-wetting behavior of the PEO/EC fibers, especially on those fiber compositions having more EC contents.

Studies showed that the initial water contact angles of the electrospun PEO fibers were lower than 90° and metastable [38,39]. In contrast to the literature data, our measurements were recorded at the immediate time (e.g., < 0.1 s) of the droplet sitting on the fiber mat surfaces prior to the capillary action on the uptake of droplet in the PEO fiber mats. In addition, our results showed that increasing EC contents in the PEO/EC fibers promoted the non-wetting behavior at the fiber mat surface due to the hydrophobic nature of the EC. This finding was similar to a study using blend fibers of poly(lactic-co-glycolic acid) (PLGA) and PEO, where the most hydrophilic composition was found to be 70PLGA/30-PEO [40]. Others reported a contact angle of 119.8 ± 1.6° for electrospun EC fibers [41], and our data were in accordance with the literature value. Overall, adjusting blend fiber compositions and

incorporating small molecular drugs at high loadings provided the effects of modifying the surface wettability on the electrospun fiber mats.

3.6. Water absorption rate measurements

During the water contact angle measurements, some fiber mats readily absorbed the 4-μL water droplets in a short amount of time. These experimental observations were associated with the blending of water-soluble PEO into the hydrophobic EC fibers, resulting in a more hydrophilic surface of the fiber mats. The addition of IBP in blend PEO/EC fibers might also influence the wettability of the fiber mats. Following the water contact angle measurements, water absorption rate measurements were performed on various blank and IBP-loaded PEO/EC fibers.

The water absorption rates of various blank and IBP-loaded PEO/EC fibers are shown in Fig. 5. Results indicated greater average water absorption rates for both blank and IBP-loaded PEO/EC fibers with EC contents that were less than 50% (i.e., more PEO in the blend fibers). Specifically, the water absorption rates for blank PEO/EC fibers at 100/0 and 75/25 compositions were 12.4 ± 1.9°/s and 13.0 ± 0.6°/s, similar to those of the IBP-loaded counterparts with 13.3 ± 0.7°/s and 12.3 ± 0.7°/s, respectively. The inclusion of PEO in EC fibers promoted the water uptake ability of the fiber mats. This phenomenon was associated with the interactions of PEO with water causing chain relaxation of the polymer matrix that increased chain flexibility allowing the matrix to swell [42]. However, this behavior was only observed for the 100/0 and 75/25 PEO/EC fibers during the period of the investigation.

In contrast, increasing EC contents to 50% and beyond in the blend fibers significantly reduced the water absorption rates to less than 0.5°/s, suggesting the predominate role of hydrophobic EC in the blend fibers. The incorporation of IBP in blend PEO/EC fibers with EC contents greater than 50% showed minimal changes on the water absorption rates of the PEO/EC fibers. PEO has been reported as an ideal candidate in promoting the dissolution of poorly water-soluble drugs [43–45], and our findings suggested the role of PEO composition in PEO/EC blend fibers on the water absorption rates, which could potentially affect drug dissolution rates. Others studied the static and dynamic water contact angles of zein/EC fibers, where a poorly water-soluble drug indomethacin (IND) was encapsulated in PEO and electrosprayed onto zein/EC fibers [46]. Results showed an approximate 20° decrease in water contact angle on the IND/PEO-loaded zein/EC fibers. Also, their results showed that the IND/PEO-loaded zein/EC fibers appeared to exhibit a decrease in water contact angle over 15 s even though the membranes maintained their appearances with minimal wrinkling and shrinkage.

3.7. Mechanical properties

Our previous studies on the mechanical properties of electrospun blend polyesters fibers suggested the effects of rule of mixtures [37]. In particular, mechanical testing of the electrospun drug-eluting fibers was able to identify the plasticizing effects as well as the drug-polymer interactions of the incorporated small molecule drugs. Therefore, in this study, we performed uniaxial tensile tests on the electrospun blank and IBP-loaded PEO/EC fibers.

Load and displacement data were obtained from the uniaxial tensile tests and representative stress-strain curves of various blank and IBP-loaded PEO/EC fibers are shown in Fig. 6. All samples exhibited an initial linear viscoelastic region where stresses increased with increasing strain followed by a yield at around 2% stain due to the localized plastic deformation. After yielding, the stress increased minimally with increasing strain followed by a maximum stress and fracture. Increasing EC contents in blend PEO/EC fibers showed a more brittle stress-strain behavior due to the differences in glass transition temperatures (T_g) of semi-crystalline PEO and EC at −56 °C [47] and 128–130 °C [48], respectively. The much higher T_g of EC provided a glassier deformation behavior at room temperature as the content of the EC increased in PEO/EC blend fibers. Interestingly, for blend fiber compositions of 100/0, 75/25, and 50/50, the IBP-loaded PEO/EC fibers appeared to exhibit a lowered stress level than the blank counterparts, suggesting the plasticizing effects of IBP in the polymer matrix [49]. This effect was not observed in PEO/EC fiber compositions of 25/75 and 0/100, where the increase in stress of the drug-loaded PEO/EC fibers could potentially attribute to drug-polymer interactions [37].

The average elastic moduli of blank and IBP-loaded PEO/EC fibers at various compositions are shown in Fig. 7(a). Increasing EC contents in the blend PEO/EC fibers increased the average elastic moduli followed by a decrease as the EC contents continued to increase for both blank and IBP-loaded PEO/EC fibers. The maximum average elastic moduli were observed at the 75PEO/25EC fibers with values reaching 23.3 ± 4.8 MPa and 32.9 ± 1.4 MPa for blank and IBP-loaded fibers, respectively. The average tensile strengths, shown in Fig. 7(b), suggested a similar trend as the average elastic moduli, where the average tensile strengths increased with increasing EC contents followed by a decrease as the EC contents continued to increase in both the blank and IBP-loaded PEO/EC fibers. The maximum average tensile strengths were found at the 50/50 composition with values of 1.14 ± 0.12 MPa and 1.18 ± 0.14 MPa for blank and IBP-loaded PEO/EC fibers, respectively. The average elongation to failures, shown in Fig. 7(c), decreased significantly when increasing the EC contents in the both blank and IBP-loaded PEO/EC fibers. The maximum average elongation to failures were observed at the 100/0 PEO/EC composition with values of 232.5 ± 29.9% and 681.8 ± 107.0% for blank and IBP-loaded PEO/EC fibers, respectively. For the remaining fiber compositions, the average elongation to failure was between 20% and 50%, except for the IBP-loaded 75PEO/25EC fibers (4.5 ± 1.9%). The significant change in average elongation to failure suggested the importance of glassy deformation behavior from EC as compared to a more rubbery deformation from PEO in the blend fibers.

The incorporation of various plasticizers and their corresponding effects on loadings in Soluplus® films (trade name of polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol grafted copolymer) were investigated, and the results showed decreases in average elastic moduli and increases in elongation to failure when increasing the plasticizer contents in the films [50]. This effect was in accordance with our findings on the IBP-loaded 100PEO/0EC fibers, suggesting that the role of IBP as a plasticizer that increased the free volume between the intermolecular PEO chains resulting in greater chain mobility with less resistance to deformation. Furthermore, incorporation of a plasticizer, such as IBP, decreased the T_g due to the enthalpic event of chain relaxation associated with the increase in free volume between the intermolecular chains [49]. Thermal studies on the incorporation of

IBP in Eudragit® RS 30 D films showed a decrease of T_g as the IBP loading increased to 25% [51]. Others showed the plasticizing effects of IBP in electrospun PLGA fibers with a decrease in elastic modulus and an increase in elongation to failure [52].

In addition to the effect of small molecule drugs as a plasticizer, the effects of nanocellulose and ampicillin on the mechanical properties of alginate films were reported [53]. Results showed that incorporation of 0.5% nanocellulose solution in alginate films increased the tensile strength and decreased the elongation to failure. The addition of 1% ampicillin in alginate and nanocellulose/alginate films further increased the tensile strength and decreased the elongation to failure. Similar to the reported finding, our data suggested a decrease in elongation to failure after incorporation of EC and IBP. However, the tensile strength of the blank PEO/EC fibers showed a significant decrease in tensile strength at high EC contents, perhaps due to the brittleness of the EC [54].

3.8. In vitro drug release rates from PEO/EC fibers

Typical in vitro drug release behaviors from electrospun drug-eluting fibers involved the wetting of the polymer fibers, where the small molecule drugs located at the fiber surfaces dissolved in the release media. The transportation of the water molecules into the fibers enabled the diffusion process of the encapsulated drugs inside the fibers driven by concentration gradient. In this study, electrospun drug-eluting fibers from blend hydrophobic EC and water-soluble PEO were expected to provide tunable release rates due to the various compositions of PEO/EC in the fibers.

The in vitro release curves of IBP from the PEO/EC fibers at various compositions are shown in Fig. 8. All samples, except the 0PEO/100EC fibers, exhibited a burst release behavior after 10 min in the release media, where the burst release rates were associated with the content of the PEO in the blend PEO/EC fibers. The cumulative releases of IBP continued to increase to reach a plateau for all fiber formulations containing PEO, suggesting the role of PEO matrix dissolution in the release media that promoted the drug release rates. In contrast, the cumulative release of IBP from 0PEO/100EC fibers gradually increased to 46.8 ± 1.0% and 87.8 ± 5.7% after 30 and 120 min, respectively. The slow release behavior of IBP from 0PEO/100EC demonstrated the diffusion-limited process in drug release from electrospun fibers.

These results demonstrated that electrospun PEO/EC fibers were capable of encapsulating IBP at a high loading (30%), while the in vitro release behaviors depended on both times and compositions of the blend fibers when using PBS/ethanol (50/50) release media due to the limitation of IBP solubility in PBS (Section 2.8). In particular, our results were in accordance with the hypothesis that water-soluble PEO promoted IBP release through dissolution process of the polymer matrix, whereas the hydrophobic EC sustained IBP release through drug diffusion. When blended, the two polymers showed miscibility and the drug release mechanisms involved both polymer matrix dissolution and drug diffusion [55]. In a study, thermosensitive poly(N-vinylcaprolactam) (PNVCL) was blended with EC and electrospun into fibers to encapsulate ketoprofen (LogP = 3.29) [56]. Results showed that the cumulative releases of ketoprofen were modulated through the pH and temperature of the release media. Others described the incorporation of PEO into zein/EC blend fibers

to accelerate the release of IND (LogP = 4.27) [46]. Furthermore, in vitro release rates of naproxen (LogP = 3.29) were modulated by blending water-soluble poly(vinyl pyrrolidone) (PVP) with EC at various compositions, where the increase of EC contents tended to slow down the release rate over 80 hrs [57]. These findings suggested the advantages of blend polymers in electrospun drug-eluting fibers, where the physicochemical properties of the blend polymers as well as the controls of the environment (e.g., pH, temperature, and composition of the release media) determined the in vitro drug release behaviors. In our study, the ability to modulate the in vitro release of a poorly water-soluble drug (i.e., IBP) from PEO/EC fibers within 120 min provided a strategy in topical drug delivery applications.

4. Conclusions

In general, our study demonstrated the ability to encapsulate a poorly water-soluble drug (i.e., IBP) at 30% (w/w) loading in electrospun blend PEO/EC fibers at various compositions. Fibers with defect-free surface morphologies were electrospun, where the average fiber diameters suggested an optimization potential on blend fiber compositions. Incorporation of the IBP showed potential optimization for the fiber production yields. Surface wettability and water absorption rate studies showed the hydrophobic effects of EC in blank and IBP-loaded PEO/EC fibers. Furthermore, mechanical testing on the blank PEO/EC fibers showed brittle deformation behavior depending on the EC contents in the blend fibers. The IBP-loaded fibers further demonstrated the effects of drug plasticization and drug-polymer interactions through various compositions of the PEO/EC fibers. Finally, in vitro release data suggested a tunable release rate of IBP supported by the wettability and water absorption rate studies. Adjusting the wettability of the fiber surface provided a direct method to control the drug release rate through drug dissolution and diffusion. Our findings suggested the ability to achieve an optimized blend fiber composition for controlled release of a poorly water-soluble small molecule drug for topical applications.

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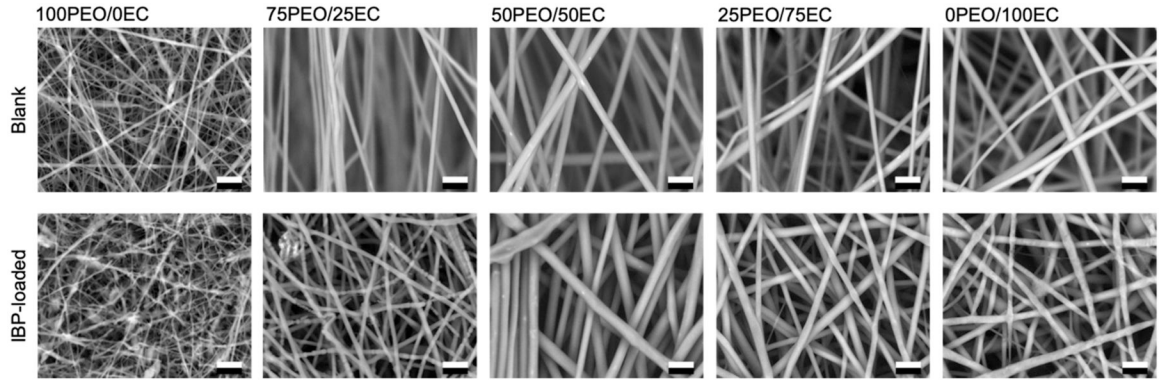

Fig. 1.

SEM images of electrospun blank and IBP-loaded PEO/EC fibers at various volumetric blend ratios. Scale bar = 10 μm.

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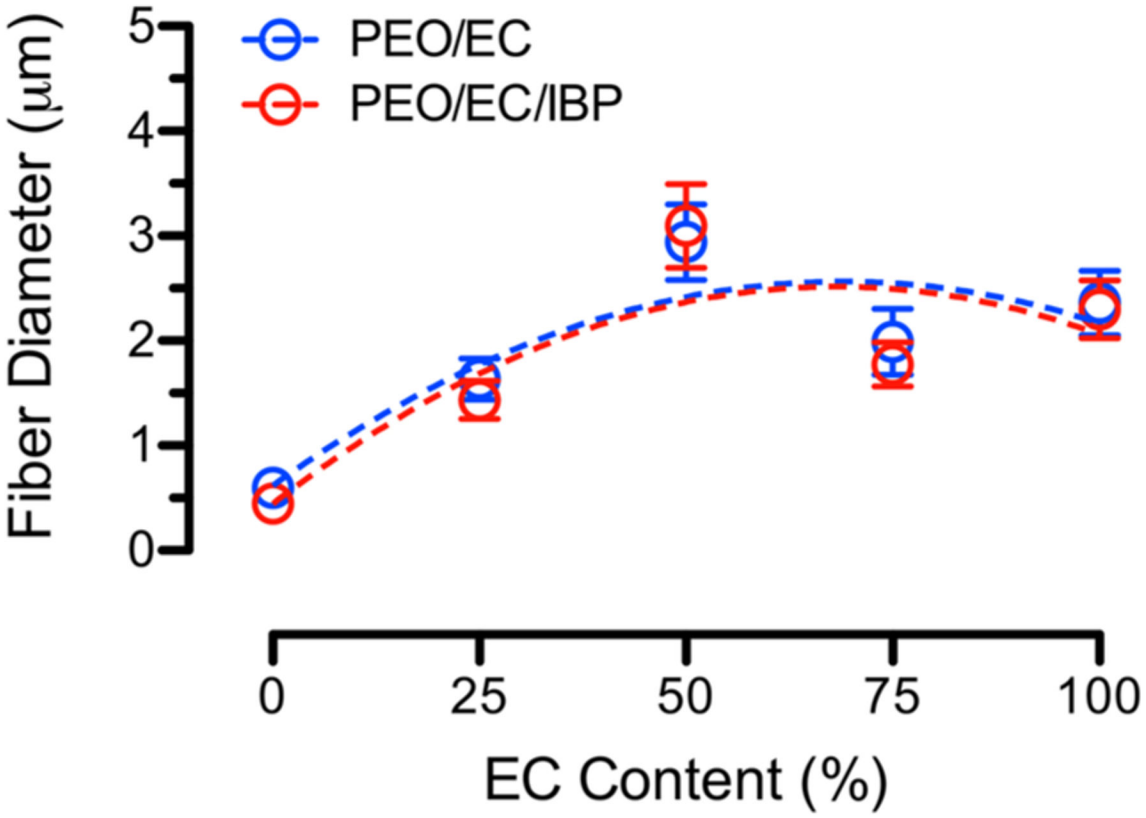

Fig. 2.
The average fiber diameters of blank and IBP-loaded PEO/EC fibers at various EC compositions.

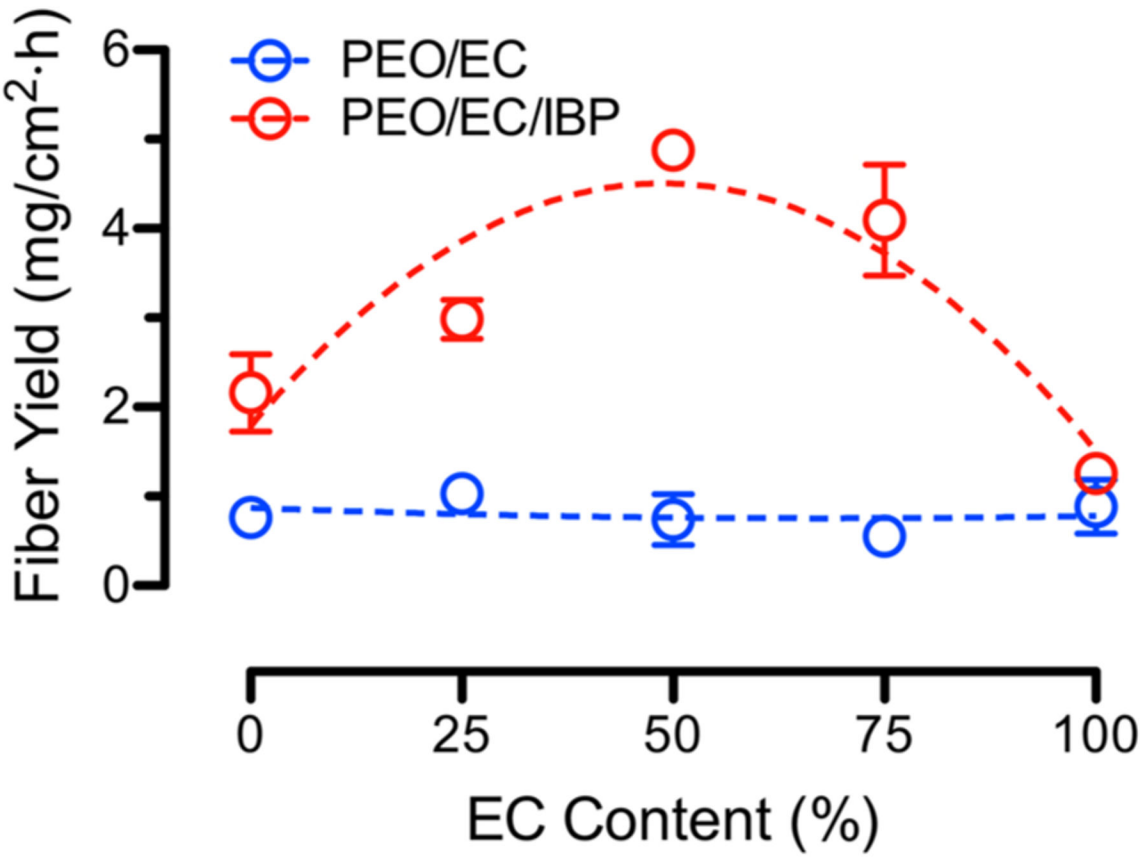

Fig. 3.
The average fiber yields of blank and IBP-loaded PEO/EC fibers at various EC compositions.

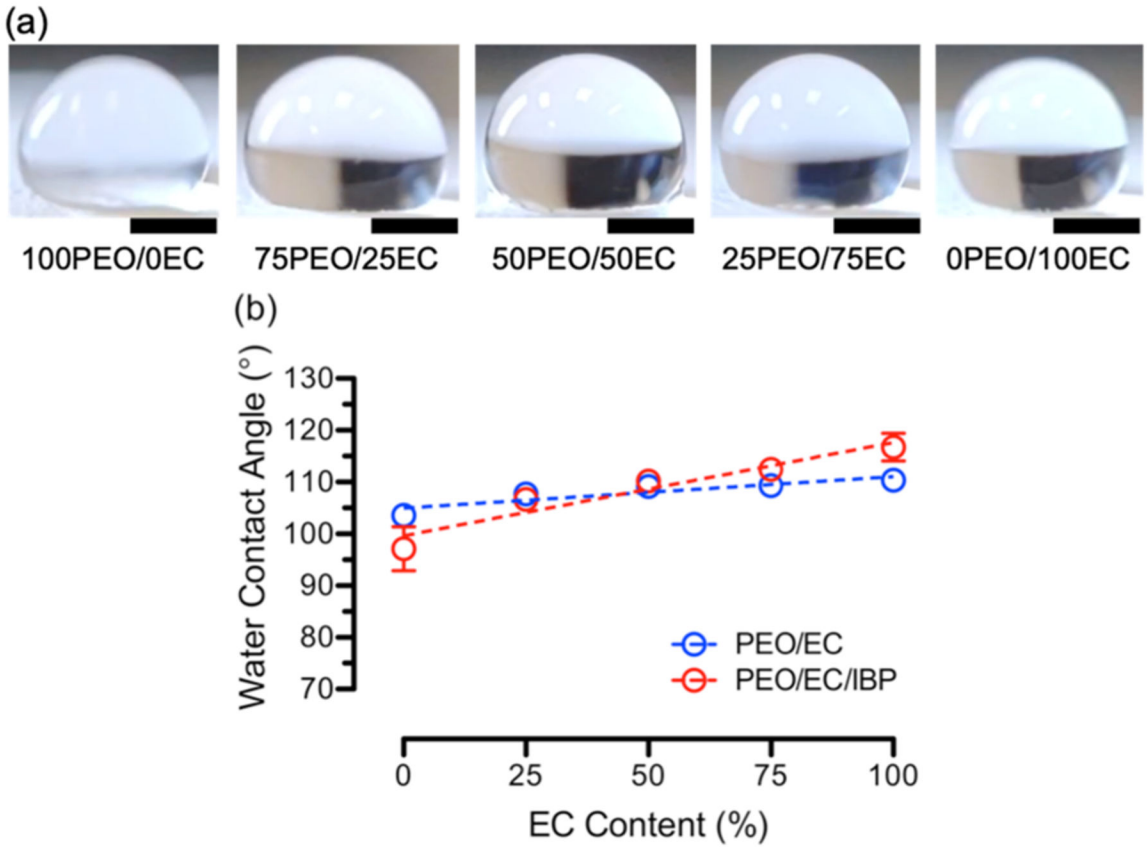

Fig. 4.

(a) Representative images of water droplets (4 μL) on the various compositions of blank PEO/EC fiber discs at t = 0 (scale bars = 1 mm). (b) The average water contact angles of blank and IBP-loaded PEO/EC fibers at various EC compositions.

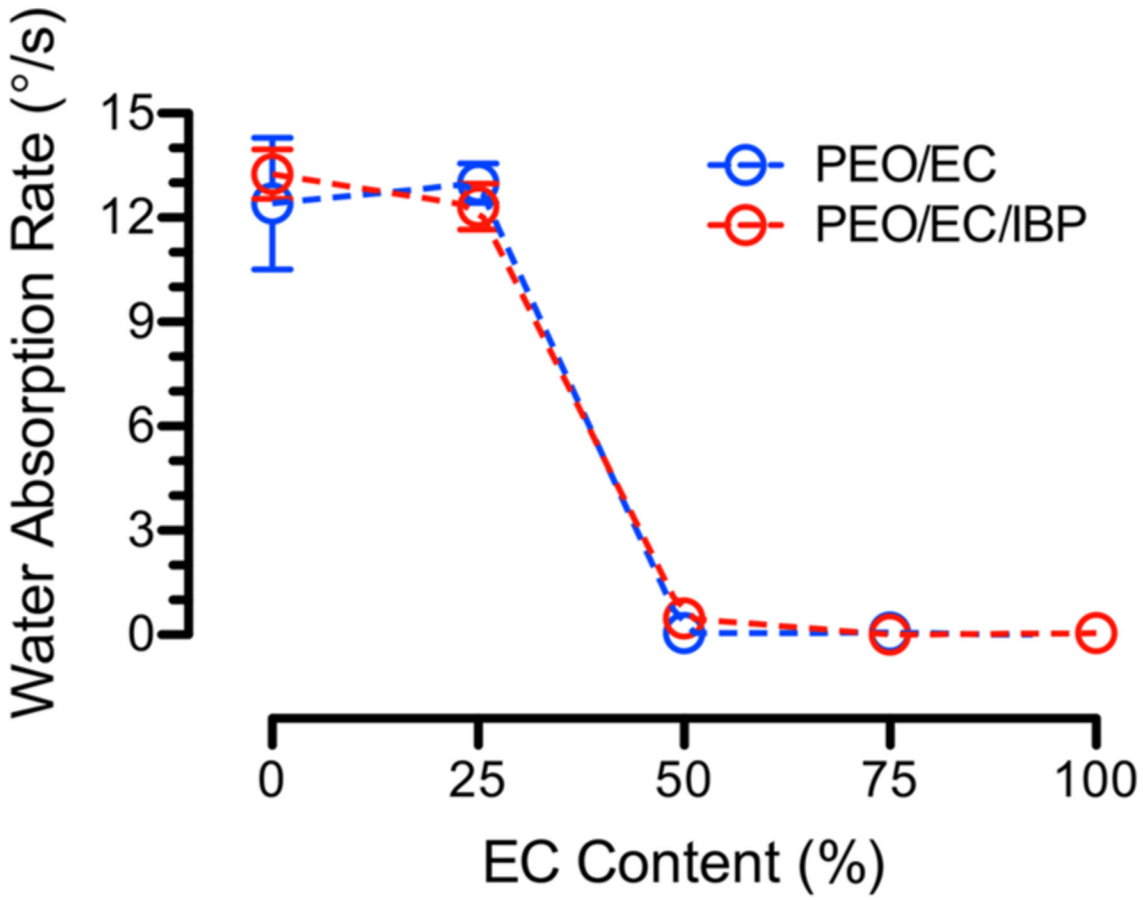

Fig. 5.
Average water absorption rates of blank and IBP-loaded PEO/EC fibers at various EC compositions.

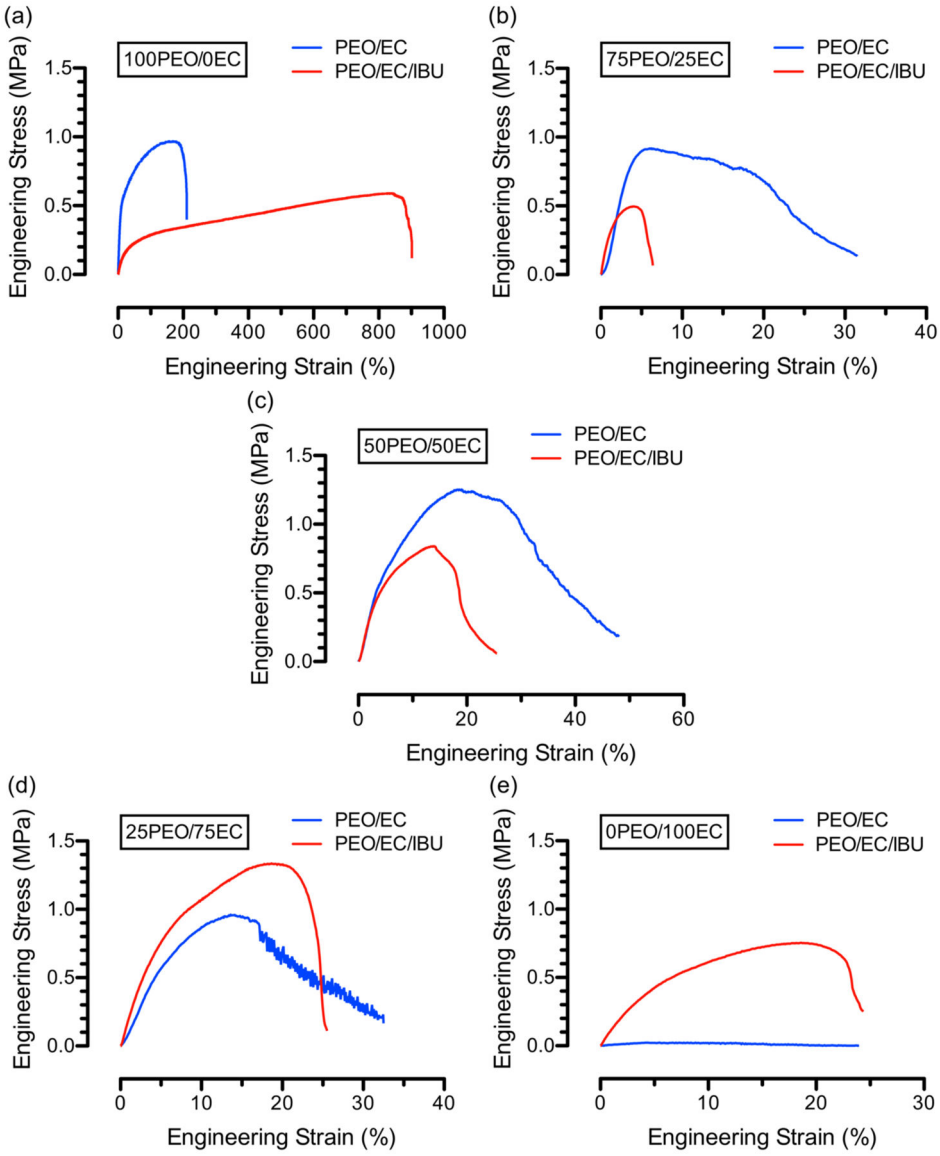

Fig. 6.

Representative engineering stress-strain curves of blank (blue) and IBP-loaded (red) PEO/EC fibers at various compositions: (a) 100PEO/0EC, (b) 75PEO/25EC, (c) 50PEO/50EC, (d) 25PEO/75EC, and (e) 0PEO/100EC.

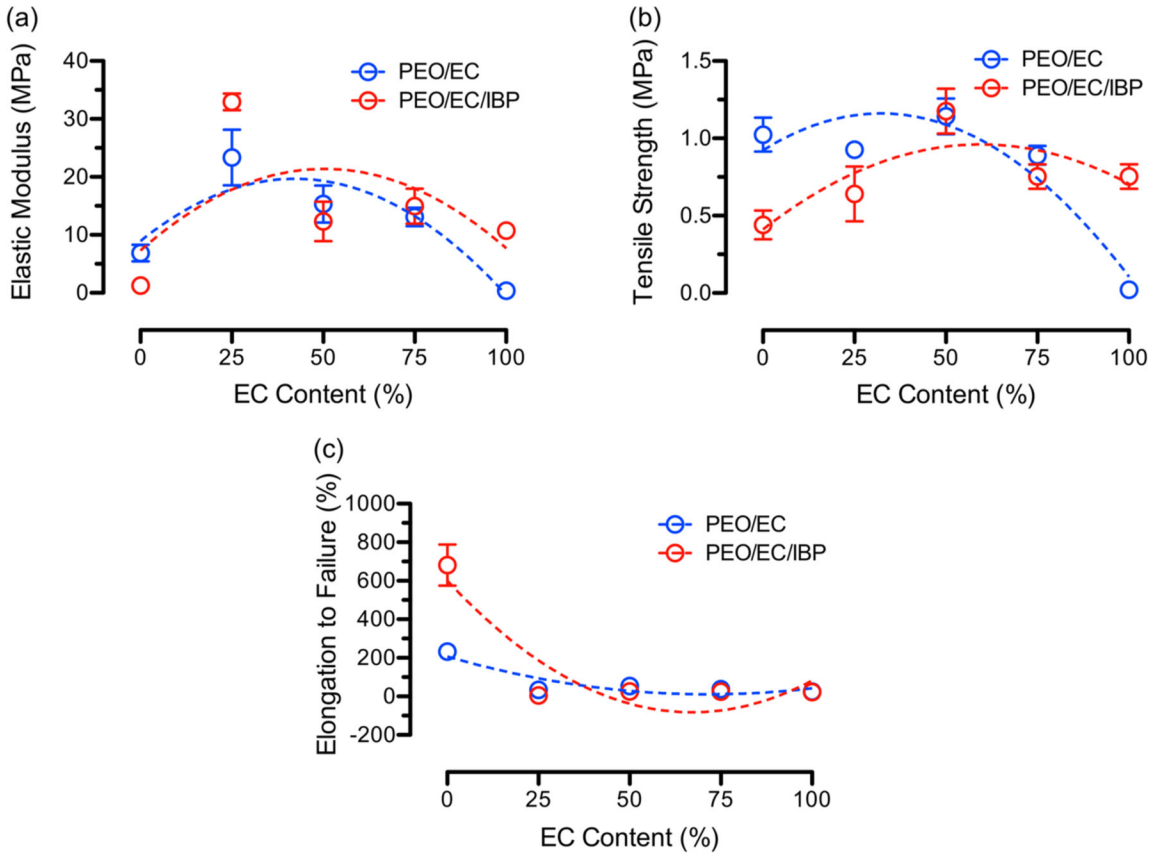

Fig. 7.

Effects of EC concentrations on the mechanical properties of electrospun blank and IBP-loaded PEO/EC fibers, showing (a) average elastic moduli, (b) average tensile strengths, and (c) average elongation to failure.

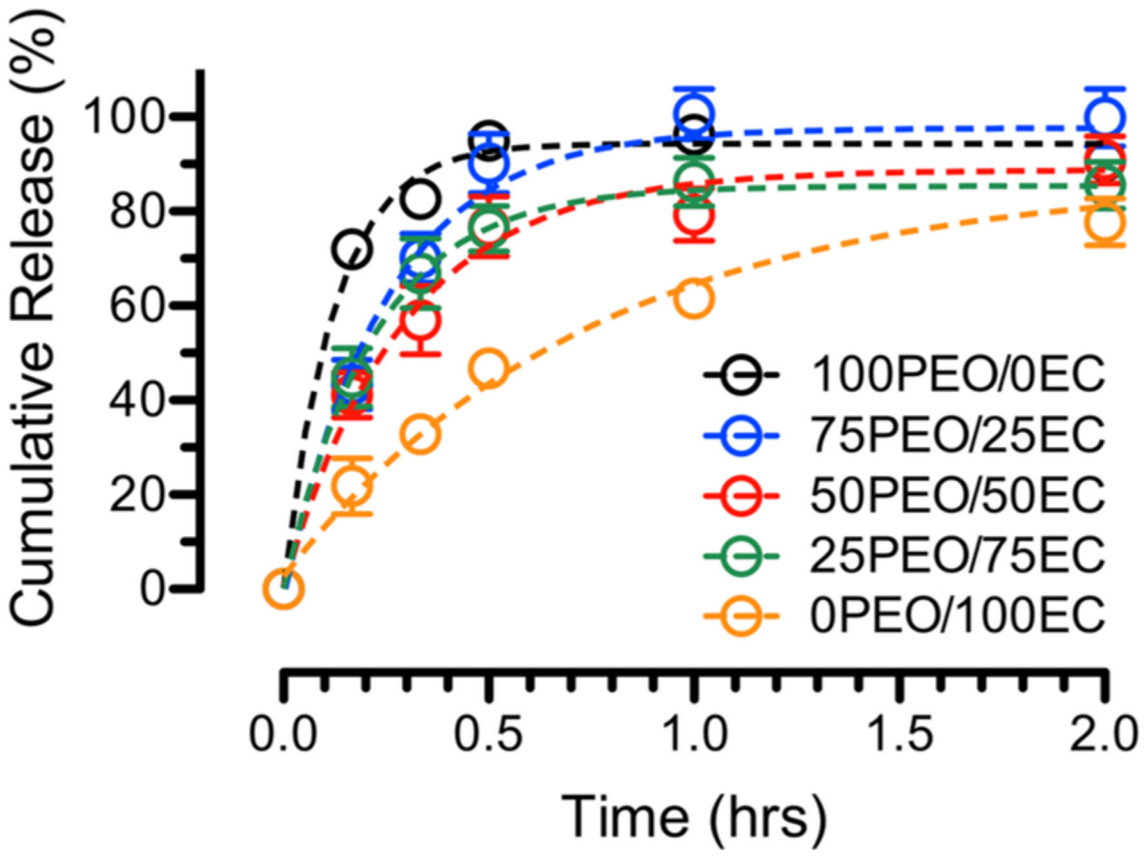

Fig. 8.

In vitro cumulative releases of IBP from various compositions of PEO/EC fibers at 30% w/w loading using PBS/ethanol (50/50) release media.