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Fabrication of a light-emitting shape memory polymeric web containing indocyanine green

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Abstract: Dye-containing polymers are highly desired for a number of commercially and medically relevant applications, such as sensors, medical devices, and drug delivery. In particular, dyes that emit light in the NIR region of the electromagnetic spectrum are of great interest due to the window of transparency for mammalian soft tissue in this range. While the incorporation of dyes into polymeric hosts by diffusion is a method that has been widely used, this approach is problematic in that it lacks uniformity and control over the incorporation. Here, we sought to develop NIR-emitting polymeric materials with high fluorescence intensity, addressing the problem of uniformity by incorporating the dye in a polymer host using dissolution in a mutual solvent and subsequent electrospinning into a fibrous web. This web could be prepared as a free-standing film, a coating or, as we will show, a shrink-wrap medical device label. The primary findings of this study were that an optimal concentration of dye in the polymer host exists, that the fluorescence intensity for fibrous webs greatly exceed that of comparable cast films, and that the dye-containing webs feature water-triggered contraction of use for application to medical devices, such as feeding tubes or catheters. © 2014 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 00B: 000–000, 2014.

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INTRODUCTION

The need exists for new ways to image implanted medical devices and surgical tools that avoid the use of potentially harmful ionizing radiation, such as that used in x-ray imaging. Near infrared (NIR) (700–1000 nm) fluorescence (NIRF) imaging is a viable non-invasive alternative owing to the relative transparency of human tissue to NIR light.[1,2] As one example application, NIRF imaging could satisfy the need for real time imaging of nasogastric tube placement in infants and adults in a non-invasive manner.

NIRF dyes are known in the art, and function by absorbing light in the near IR portion of the optical spectrum and emitting light (in response to this) at a different wavelength, also in the near IR portion of the optical spectrum. Near-IR light is particularly applicable for medical applications, as mammalian tissue is particularly transmissive in this portion of the optical spectrum, indicating that it may be useful surgically.[1–3] One way to achieve medical devices that exhibit NIRF behavior would be to use a "guest-host" approach in which NIR dye or nanoparticle guest is incorporated in some manner within a polymeric host that serves other functions of the device. Indeed, polymers containing nanoparticles or dyes are highly desired for a number of commercially and medically relevant applications, including highly sensitive sensors,[4,5] medical devices, and drug delivery. However, no method is available to effectively incorporate NIRF dyes into polymeric articles without manipulating their fluorescence properties, a limitation this study addresses.

Incorporation of dyes by diffusion,[6] compression-molding,[7] and blending[8] are methods that have been reported; however, some of these approaches are problematic in that they lack uniformity and control over the incorporation. Consequently, the bright emission of dyes from the polymer is not uniform. As we will show in this article, electrospinning is a viable technique to uniformly incorporate dyes without manipulating the property of dyes. Electrospinning is a widely used technique to fabricate nanofibers from thermoplastic polymer solutions. To the best of our knowledge, only Bianco et al. demonstrated uniform optical property of electrospun light emitting polymers, but they did not use any dye in their study.[9] It is further desirable to incorporate dyes with specific optical absorption and emission characteristics into thermoplastic polymer hosts in order to yield light-activated polymers that are easily imaged in medical applications. For example, incorporating indocyanine green (ICG) dye, which has a near-infrared (NIR) excitation

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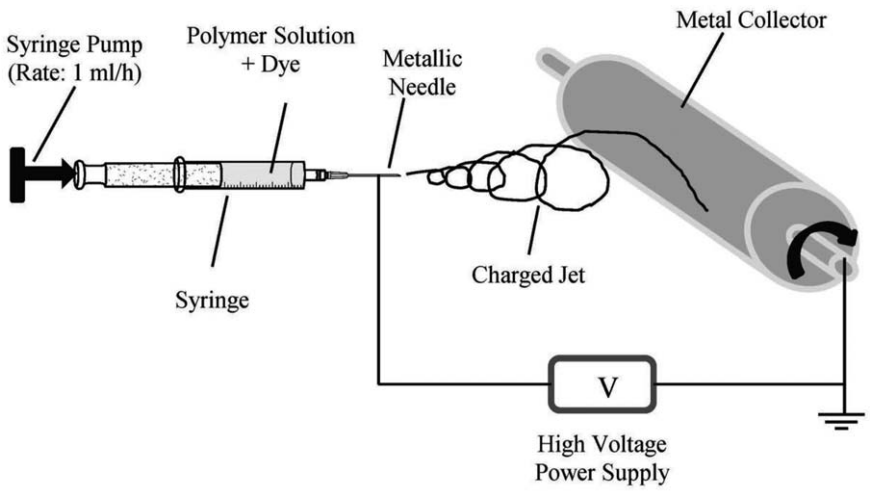


SCHEME 1. Schematic of electrospinning device.

and emission wavelength, into a polymeric medical device would allow that device to be easily detected for spatial location using an NIRF imaging system, noting that ICG's strongest absorption band is around 700 nm and the most intense emission of ICG is around 800 nm.[10,11] Tracking the position of pediatric catheters or epidural catheters during use is of great interest, especially in cases where coiling or kinking of these flexible catheters can occur, causing serious complications in patients.[12] The present study offers a method to uniformly incorporate ICG dye at different concentrations into a thermoplastic polymer via electrospinning, demonstrating its utility in imaging and unique shape memory properties of use for application to catheters by shrink-wrapping. It is noted that ICG is a FDA-approved biocompatible dye which has been used in humans and for vascular and tumor studies for over 50 years.[13–15]

In this article, we report our findings by first showing uniform incorporation of near-infrared fluorescence (NIRF) dye into the thermoplastic polymers via electrospinning. We also demonstrate that the electrospun webs of a particular polymer shrink upon heating or hydrating, indicating that electrospinning itself provides a means to fix a temporary shape of this particular shape memory polymer (SMP) and utility for application to tubing. We demonstrate implementation of the shrinkage phenomenon in the form of facile application of NIR-fluorescent markers to such surgical and medical devices as catheters, guidewires, and feeding tubes.

EXPERIMENTAL SECTION

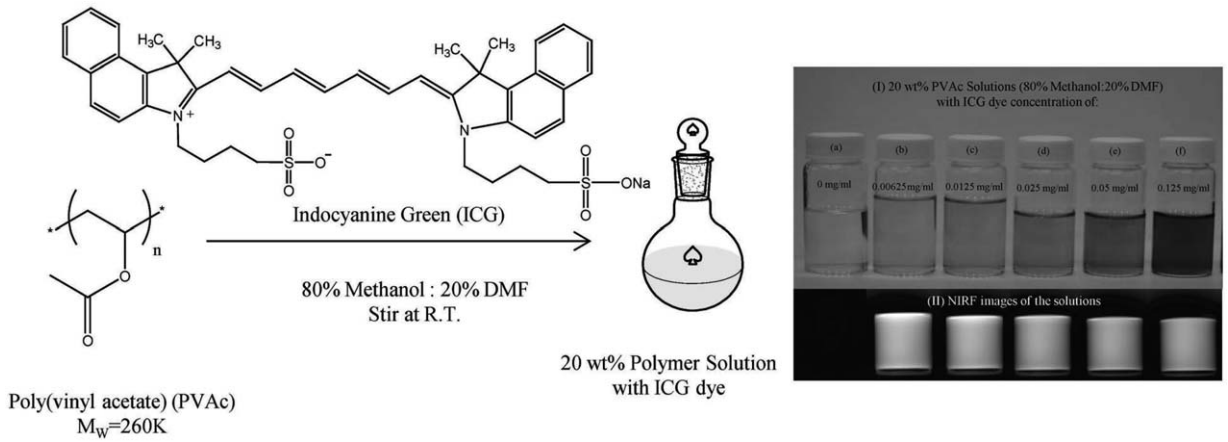
Materials

Poly(vinyl acetate) (PVAc) ($M_w = 260{,}000$ g/mol) was purchased from Scientific Polymer Products, Inc. Indocyanine green (ICG) (Cardiogreen) and N,N-Dimethylformamide (anhydrous, 99.8) (DMF) were purchased from Sigma Aldrich. Methanol was purchased and used as received from Fisher Scientific.

Electrospinning method

Electrospinning is a widely used technique to fabricate nanofibers from thermoplastic polymer solutions.[16–19] Scheme 1 shows a diagram of the electrospinning device used for our study. Under the influence of an electric field, electrostatic charges build up on the surface of the liquid meniscus pumped from the needle tip and a charged jet forms continuously. Then the charged jet is stretched to form continuous fibers on the metal collector, the Rayleigh instability being suppressed by solvent evaporation that occurs before the charged jet has reached the collector. Polymer solutions appropriate for electrospinning can be prepared by dissolving nearly any thermoplastic polymer in its respective solvent and then tuning concentration.[17–19] For our electrospinning process, polymer solutions were loaded into a glass syringe bearing a metal needle that is connected to the high voltage power supply. The collector was grounded and rotates at a speed of 300 rpm. The electrospinning was then performed at a voltage of 8 kV, with 7 cm distance between the needle tip and the surface of the collector drum with diameter of 5 cm. The flow rate of each polymer solution was maintained at 1 mL/h by a syringe pump (KDS100, KD Scientific).

Here, poly(vinyl acetate) (PVAc) ($M_w = 260{,}000$ g/mol) and different concentrations of indocyanine green (ICG) were dissolved in a solution containing 80% methanol and 20% N,N-dimethylformamide (DMF) to generate a 20 wt % polymer solutions with ICG concentrations of 0, 0.000625, 0.0125, 0.025, 0.05, 0.125 mg/mL (Scheme 2). For example, to prepare the electrospinning solution with ICG concentration of 0.0125 mg/mL, two solutions were separately prepared and then combined. A polymer solution containing 2 g of PVAc in 7 mL of methanol was prepared and later combined with a solution of 0.125 mg/mL of ICG in 1 mL of methanol. Finally, this combined solution was diluted with 2 mL of DMF in order to enable electrospinning. Each electrospinning solution was then loaded into a glass syringe and electrospun to fabricate nanofibers containing the ICG dye. Using this technique, uniform dye incorporation was achieved. Films containing the same concentrations of dye were prepared for comparison purposes by solvent casting. Here, solutions as described above were cast into



SCHEME 2. Procedure of incorporating ICG dye into the polymer solution. (I) The photograph of the solutions at ICG concentrations of (a) 0 mg/mL, (b) 0.00625 mg/mL, (c) 0.0125 mg/mL, (d) 0.025 mg/mL, (e) 0.05 mg/mL, and (f) 0.125 mg/mL. (II) The NIR images of the same vials under the NIRF imaging system at the gain of 1 and exposure time of 150 ms.

rectangular Teflon® molds, followed by slow evaporation in a fume hood for 12 h. Subsequently, electrospun fiber mats and cast films were placed in a vacuum oven for 24 h at room temperature to evaporate any residual solvent.

Characterization

Scanning electron microscopy. Scanning electron microscopy (SEM); (JEOL JSM5600) was utilized at an accelerating voltage of 6 kV to study the morphology of each electrospun fiber mat. Prior to the SEM analysis, samples were sputter coated with gold for 45 s. ImageJ software (U.S. National Institutes of Health, Version 1.47) was used to calculate the average fiber diameters from total number of 90 fibers selected randomly from each SEM image.

NIRF imaging. A custom-built NIRF imaging system shown in Figure 1 was utilized to characterize NIR fluorescence of all samples. The fiber optic ring light was coupled to a 150W Tungsten Halogen EKE-ER lamp (Illumination Technologies) filtered with a bandpass filter centered at 785 nm (Semrock). A CCD camera from QImaging Corp equipped with Semrock band-pass filter (835 ± 37 nm) was used to capture the images. All the images were acquired from the camera at room temperature with a gain of 1.0 and exposure of 140 ms using QCapture Pro software. ImageJ software was utilized to analyze and calculate the mean gray values for each image.

Fluorescence spectroscopy. Fluorescence spectroscopy was further utilized to determine the intensity of excited ICG dye incorporated into the polymer via casting and electrospinning. The measurements were collected on an Agilent Cary Eclipse fluorescence spectrophotometer equipped with a microplate reader. The excitation wavelength used for the experiment was 700 nm using 5 nm excitation and emission slits at the detector voltage of 1000 V.

RESULTS AND DISCUSSION

Numerous reports have been published on incorporating dyes into polymer films and into electrospun polymeric nanofibers by diffusion from an immersion solution[6] or casting polymer solutions. However, to our surprise, no reports exist concerning the more direct process of electrospinning of thermoplastic polymers with the dye of choice by dissolving the dye in the polymer solution being electropun. Of course, the process by which dye is incorporated may have a significant difference on the distribution of dye in the material. For example, diffusion of dye into the fibers of an electrospun web will naturally lead to non-homogeneous concentration gradients from fiber surface to fiber core. This problem is further compounded in films due to the larger diffusion length scale of the film or coating thickness and in hydrophobic polymers due to limitation of diffusion. In contrast, electrospinning a molecularly

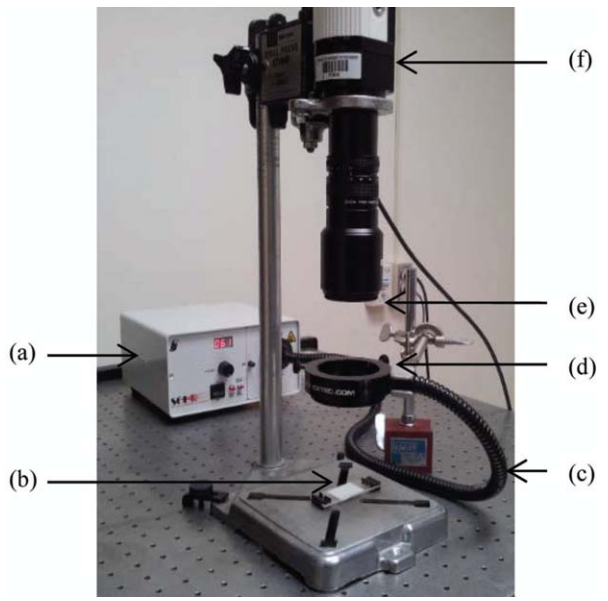


FIGURE 1. NIRF imaging system used for fluorescence imaging: (a) tungsten halogen light source (150 W), (b) Specimen, (c) fiber optics, (d) ring light source (785 nm), (e) band-pass filter (835 ± 37 nm), and (f) camera. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

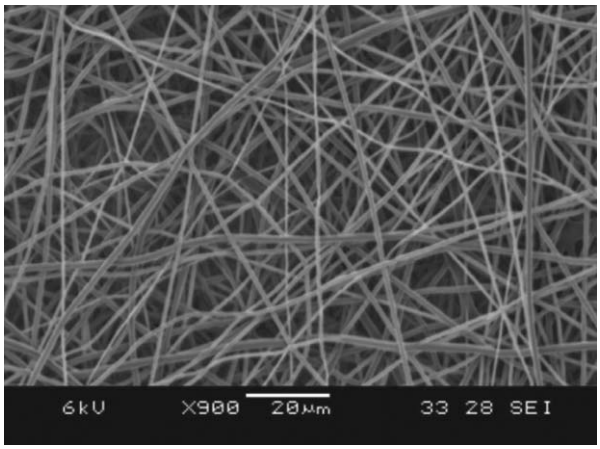


FIGURE 2. SEM image of electrospun PVA/ICG with the ICG concentration of 0.025 mg/mL with an average fiber diameter of 0.86 ± 0.22 μm (n=74). ImageJ software was utilized to calculate the average fiber diameter.

homogeneous solution of dye and polymer dissolved in a mutual solvent should lead to uniform distribution of dye across the cross-section of each constituent fiber. Furthermore, there are no limitations to incorporation of thermally sensitive dyes in this technique since the process is conducted at room temperature. It was in the context of these expected benefits that we adopted the new approach. In doing so, however, we unexpectedly found that the fluorescence intensity of dye incorporated into nanofibers was dramatically higher than when incorporated in films of the same host polymer. This effective increase in intensity is important to the successful utilization of NIRF-emitting materials in the imaging for medical devices and for other applications.

The morphologies of the electrospun fibers were examined using SEM, each composition yielding very similar results. The morphology of electrospun PVAc with the ICG concentration of 0.025 mg/mL is shown in Figure 2, as a representative result. SEM images of other fiber mats with different concentrations are not shown, as they are morphologically similar. Uniform fibers with an average fiber diameter of 0.86 μm and standard deviation of 0.22 μm ($n = 74$) were achieved for this composition and similar observations were made for other compositions with no systematic dependence on ICG concentration.

NIRF imaging and spectrofluorometry have been utilized to compare polymer fiber mats and casted polymer films containing different concentrations of ICG dye. Photographs and NIRF imaging results of PVAc fiber mats with different ICG concentration and cast PVAc films with different ICG concentrations are shown in Figure 3. Generally, the fiber mats showed higher fluorescence intensity and uniform dye incorporation compared to the cast films. In order to further analyze and compare images shown in Figure 3, we measured the mean gray values of images for each sample using ImageJ software. These results will be discussed below, along with spectrofluorometry data, in reference to Figure 5.

Spectrofluorometry of PVAc fiber mats and casted PVAc films with different ICG concentrations are shown in Figure 4. Samples were illuminated with an excitation wavelength of 700 nm and the highest emitted intensity was measured at the wavelength of 800 nm. Interestingly, we observed non-monotonic dependence of NIRF intensity on ICG concentration with maximum intensity appearing at an intermediate concentration, suggesting that at high dye concentration quenching occurs, resulting in lower emission and a near-linear relationship between dye concentration

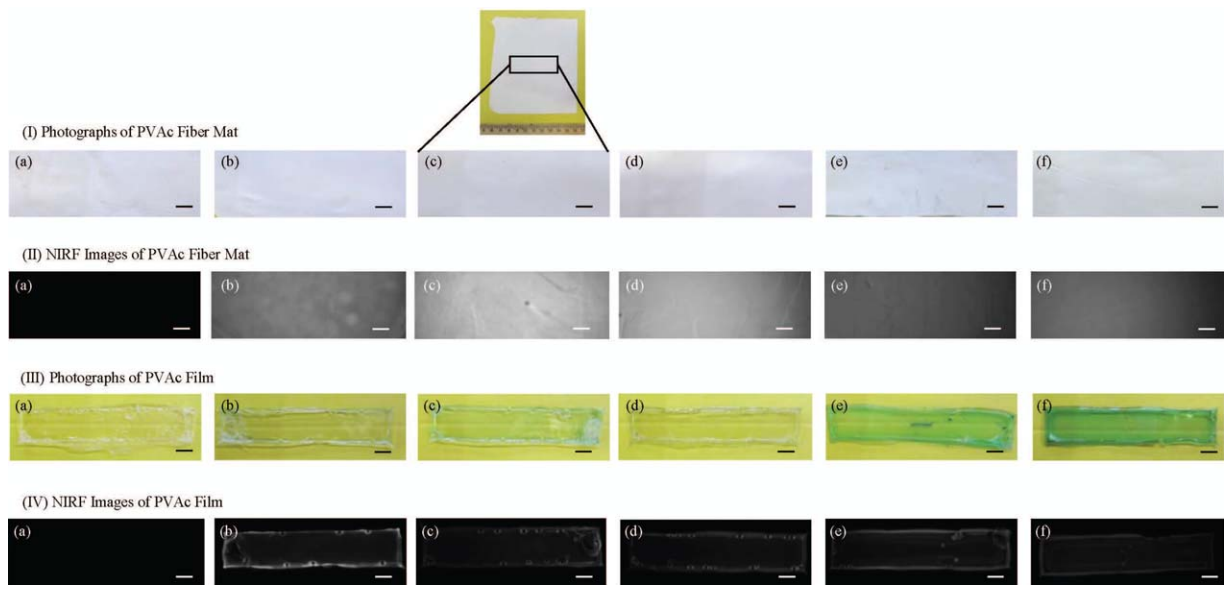


FIGURE 3. (I) Photographs of PVAc fiber mat, (II) NIRF images of fiber mat, (III) photographs of PVAc film, (IV) NIRF images of PVAc film, each with ICG concentrations of: (a) 0 mg/mL, (b) 0.00625 mg/mL, (c) 0.0125 mg/mL, (d) 0.025 mg/mL, (e) 0.05 mg/mL, and (f) 0.125 mg/mL. The gain and exposure time were 1 and 140 ms respectively. The scale bars each represent 5 mm. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

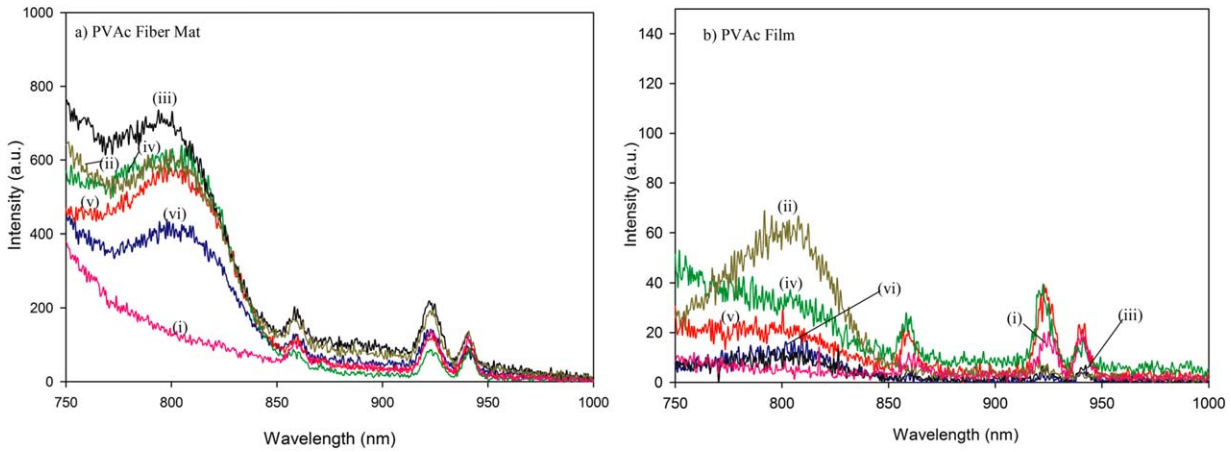


FIGURE 4. Spectrofluorometry of (a) PVAc fiber mat with different ICG concentration, and (b) PVAc films with ICG concentration of (i) 0 mg/mL, (ii) 0.00625, (iii) 0.0125, (iv) 0.025, (v) 0.05, and (vi) 0.125. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

and fluorescence at low concentrations. We attribute the fluorescent bands at 860, 923, and 940 nm to NIR autofluorescence of PVAc, though we could find no prior report on such an observation.

Our findings obtained from both NIRF imaging and spectrofluorometry analysis were used to compare emission intensities for polymer fiber mats and cast polymer films over a range of ICG concentration. Figure 5 shows graphs that compare emission intensities for PVAc fiber mats and PVAc films with different ICG concentration by using NIRF imaging [Figure 5(a)] and spectrofluorometry [Figure 5(b)] as a function of concentration. We note that the mean gray values indicating intensity were computed by using ImageJ. As mentioned above, the PVAc fiber mats showed significantly higher intensity, whether measured by spectrofluorometry or by NIRF imaging, than the PVAc films. Moreover, the existence of an optimum dye concentration was evident from the trends, the highest NIRF emission intensities being observed for samples with 0.0125 mg/mL ICG concentration. It is important to note that the concentration of dye in the fiber mats is the same as that of the solutions used to prepare those mats. This was proven using optical absorbance at 790 nm for a range of dye concentrations before and after electrospinning, the latter after re-dissolution (Supporting Information).

The origin of an optimal ICG concentration may be revealed by considering dye/polymer interactions. Indeed, the interaction of ICG with polymers has been studied and well understood by other researchers. Non-covalent intermolecular forces such as electrostatic, hydrogen bonding, and Van der Waals interactions[20] and hydrophobic interaction[21,22] are the main origin of ICG and polymer interaction. Many studies used interactions between ICG and polymer interactions to stabilize, or immobilize the ICG.[20] As we observe apparently uniform and stable fluorescence in the ICG/PVAc fiber mats, we reason that the interactions between ICG and PVAc are strong. We postulate that the uniformity of dye in fiber mats and higher scattering of

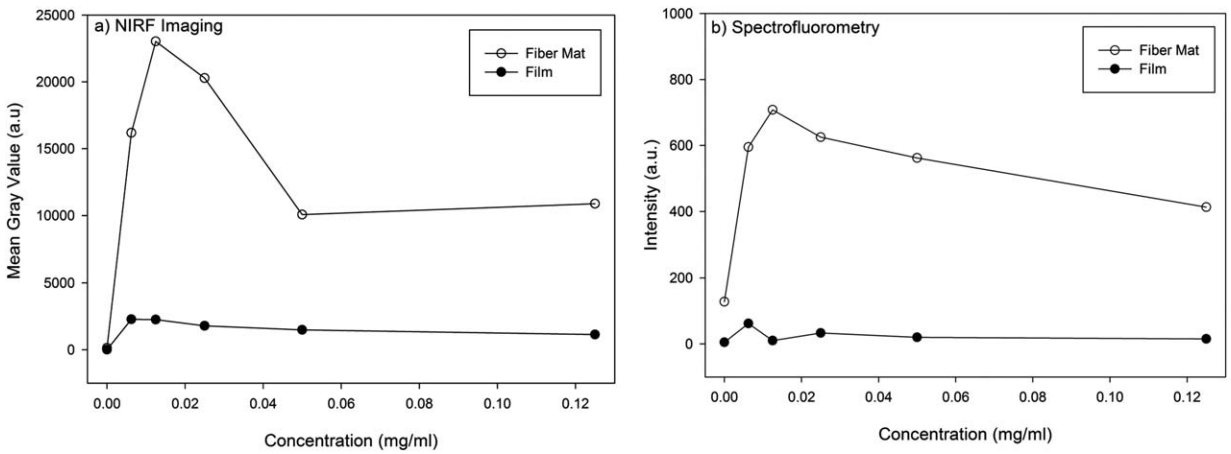


FIGURE 5. Graph of comparison of PVAc fiber mat and PVAc film with different ICG concentration by using (a) NIRF imaging and (b) Spectrofluorometry. The mean gray values were computed by using ImageJ program. PVAc fiber mat showed higher intensity and mean gray values compared to the PVAc film. The highest intensity by spectrofluorometry and the highest mean gray value by NIRF imaging were observed for samples with 0.0125 mg/mL ICG concentration.

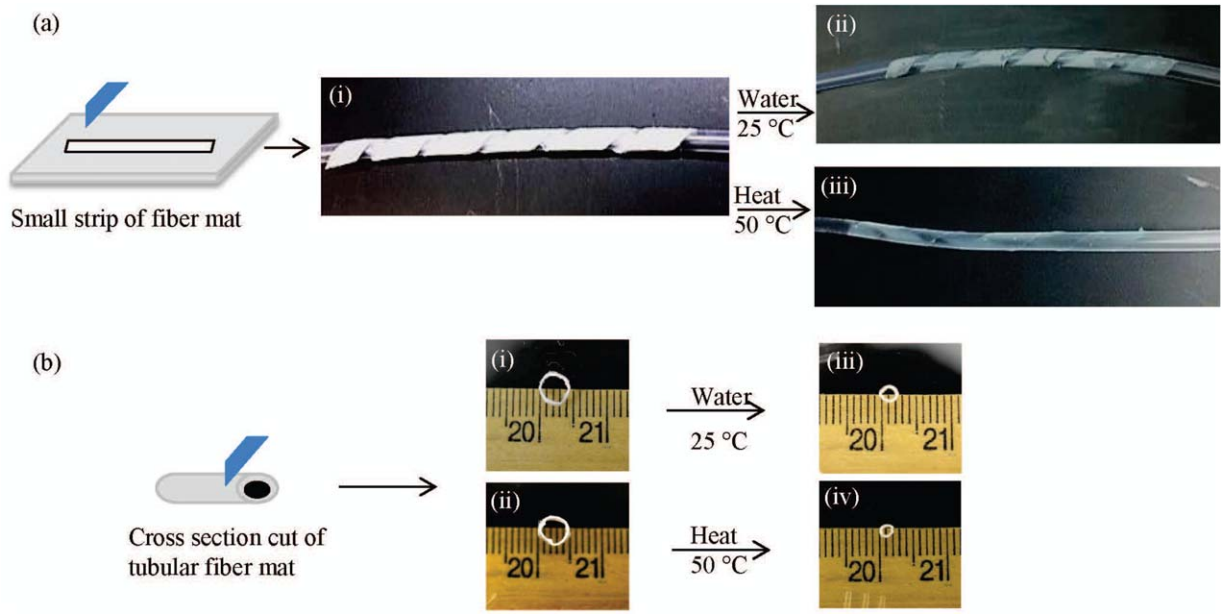


FIGURE 6. (a) A small strip was cut from the electrospun fiber mat and then wrapped around a pediatric catheter tube (i). The strip was shrunk on to the tube by applying (ii) 25°C water or (iii) 50°C heat. (b) Small rings were cut from a halo tube of electrospun fiber mat [(i) and (ii)] and recovered by applying (iii) 25°C water and (iv) 50°C heat. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

emitted light increases the intensity through multiple scattering effects.

We observed in separate experiments that PVAc fibrous webs prepared by electrospinning with the indicated method, with or without dye, exhibited significant shrinkage when heated above approximately 50°C or when immersed in water, the former being faster (Figure 6). This phenomenon can be explained by consideration of the shape memory effect in polymers. Shape memory polymers (SMPs) are polymeric networks that feature a permanent, stress-free state and a multitude of temporary shapes fixed by mechanical manipulation in a rubbery state (above T_m or T_g, termed "triggering temperature"), followed by cooling.[23,24] An environmental stimulus can be applied to trigger a shape transition from temporary to permanent shape. Highly entangled polymers can feature a shape memory, entanglements serving as physical crosslinks if their lifetime is longer than the deformation time.[24,25] Ordinarily, fixing is achieved either by deformation above the shape memory triggering temperature or slightly below the same. In the present case, we interpret the heat and water-triggered contraction as evidence that electrospun PVAc features frozen-in molecular orientation along the fiber axes similar to stretching polymer chains in SMPs. This molecular orientation is apparently relaxed upon heating to a temperature above T_g or plasticization of T_g to a value less than room temperature by water.

The shrinkage of strips of electrospun PVAc fiber mat and small rings (cut from a hollow tube of electrospun fiber mat) upon heating or contacting water is shown in Figure 6. Small strips were cut from the electrospun fiber mats and then wrapped around a pediatric catheter tube to demonstrate shrinkage by applying 25°C water or 50°C heat. The ring shrinkage in either case was 55% enabling use of the

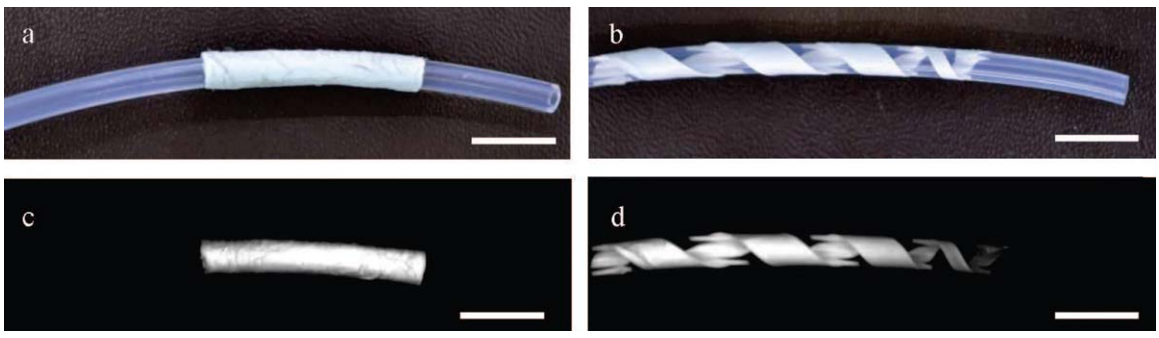


FIGURE 7. (a) and (b) are photographs of electrospun tube and small strip cut from electrospun fiber mat of PVAc/ICG with the ICG concentration of 0.0125 mg/mL wrapped around a pediatric catheter tube. (c) and (d) are the NIRF images of same devices taken with the gain of 1.0 and exposure time of 140 ms. The scale bar represents 10 mm. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

dye-incorporated fibers as a "shrink-wrap" film or band. Such combination of high-intensity NIRF emission and heat or water-triggered shrinkage can enable facile NIRF labeling of medical devices to be imaged during surgical use with NIRF equipment.

The NIRF excitation and emission of ICG dye embedded in the polymer may allow for tracking of medical devices, even within the human body, by using an NIRF imaging system. As stated previously, this approach is less invasive than other imaging techniques such as X-ray and MRI. To demonstrate an element of this, an electrospun tube of PVAc/ICG and a small strip cut from electrospun fiber mat of PVAc/ICG (ICG concentration of 0.0125 mg/mL) was applied on a pediatric tube, using water to trigger shrinkage as shown in Figure 6, and NIRF images were obtained at the gain of 1.0 and exposure time of 140 ms. As shown in Figure 7, NIRF images taken with the NIRF system display the fluorescence PVAc/ICG tube and strip on a pediatric catheter with high fidelity. It is important to observe that the pediatric tubes are invisible under the NIRF system while the PVAc/ICG coatings brightly fluoresce. The NIR fluorescence capability of the fabricated PVAc/ICG polymer combine to yield a viable candidate for marking medical devices for the purpose of tracking with a non-invasive NIRF imaging systems.

Another application of electrospun PVAc-containing ICG is laser-activated contraction so far achieved by heat and water (Figure 6). Indeed, similar light-activated SMP recovery has been studied previously by other researchers.[26,27] In this case, the intensity of incident NIR radiation is higher than that used for imaging. Using higher intensity incident NIR light than is used for imaging, the materials are expected to heat up due to non-radiative decay and once the temperature exceeds T_g they will shrink, bend, twist, or contract, depending on configuration. A surgical application envisioned for such a light-activated SMP is internal suturing, where the suture itself can be located by NIRF imaging and then activated (partially or completely) from outside the body by using NIR irradiation. This would allow tightening of loosened knot of sutures without the need for an open incision. Indeed, periodic and continued contraction of subcutaneous sutures as described may be useful for plastic surgery. Other potential applications of the PVAc fiber mat with incorporated ICG include antimicrobial medical devices,[6] packaging, drug delivery, and temperature sensors.[4] Such studies are needed in the future.

CONCLUSIONS

Incorporation of ICG dye into PVAc polymer was achieved using the electrospinning technique, yielding NIRF polymeric material with high fluorescence intensity and uniform dye incorporation. NIRF dye-containing fibrous mats of ICG in PVAc showed significantly higher fluorescence intensity when compared to the films, whether measured by spectrofluorometry or by NIRF imaging. The existence of an optimum dye concentration was evident from the trends, the highest NIRF emission intensities being observed at 0.0125 mg/mL dye concentration. Application of heat or water to the as-prepared webs exhibited significant shrinkage useful for shrink-wrap application to catheters. We envision other potential applications of the PVAc fiber mat with incorporated ICG dye include internal suturing, antimicrobial medical devices, packaging, drug delivery, and temperature sensors. Future work includes assessment of biocompatibility and fluorescence stability of PVAc/ICG in animal, antibacterial study, and investigation of light-activated shape memory.

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