Controlled release of the insect repellent picaridin from electrospun nylon-6,6 nanofibers

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Conventional insect repellent treatments for fibers, fabrics, and garments suffer from limited durability to repeated laundering and, depending on the insecticide, potential irritation, or toxicity. In this work, electrospinning was employed to control the composition of hierarchically structured functional microscale to nanoscale fibers for tunable insect repellent release by physically incorporating picaridin into nylon-6,6 nanofibers. The size and morphology of nylon fibers were unaffected by picaridin incorporation, even at loading concentrations up to 50 wt%. Picaridin release kinetics were largely dependent on loading concentration and temperature, as picaridin-nylon intermolecular interactions were minimal affording diffusion based release. Coaxial nanofibers, in which the sheath component has potential to protect additives in the core for more durable fabrics and act as a diffusion barrier for extended release applications, were also developed and demonstrated altered release kinetics compared to monofilament analogues, indicating the capability to further tune release behavior.

KEYWORDS
fibers, insect repellent, nylon, picaridin, timed release

1 | INTRODUCTION

Biting arthropods (eg, mosquitos and ticks) not only present incessant irritation, but also function as significant vectors that spread disease among populations. Other than physical barriers such as mosquito netting, the most successful method to reduce insect bites has been the application of chemical-based repellents, often aerosol-type spray or topical lotion, that deter insects from a particular area or person.1 Currently, there are several repellents approved by the FDA, of which N,N-diethyl-meta-toluamide (DEET) is the most popular, followed by 1-(1-methylpropoxycarbonyl)-2-(2-hydroxyethyl)piperidine (Picaridin), ethyl N-acetyl-N-butyl-β-alanine (IR3535), and other essential oils.2 The repellent mechanism for each insect repellent differs. For example, DEET has been proposed to repel insects through multiple mechanisms, both through avoidance via olfactory binding and as an olfactory confusant by masking the host’s odors.3,4 Picaridin interacts with similar olfactory binding sites as DEET due to structural similarity, but also binds to other novel sites providing a slightly different mode of action.5 In contrast, (3-phenoxypyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate (Permethrin) is an effective insecticide that kills insects and ticks through neurotoxic means.1 Compared to DEET, picaridin exhibits comparable repellency against both mosquitos and ticks,6,7 yet picaridin has lower toxicity, less skin irritation, better compatibility with plastics, and slightly longer duration.8

An inherent limitation to insect repellents is their finite efficacy time due to evaporation of the liquid-based repellents. A common strategy to combat this limitation has been to control the repellent release rate and/or to provide a reservoir from which to draw additional repellent. Polyester fabrics were modified to exhibit repellency by modification with complexed DEET with a cyclodextrin and grafting through an anhydride that demonstrated improved resiliency to washing with detergents.9 A common approach is to mix the insect repellent directly into a polymer solution prior to production into a fiber or coating. For example, DEET was incorporated into polyactic acid fibers via coextrusion for potential textile applications, where
DEET reduced mechanical properties of the PLA fibers while only contributing minor repellent effects.\textsuperscript{10} Modified polymer coatings are also employed to impart insect repellents to existing materials. Recently, applications of DEET and IR3535 polymer-based coatings to netting were demonstrated to provide a physical barrier that also exhibited repellent properties that lasted up to 29 weeks.\textsuperscript{11} Another approach is the incorporation of particles, or capsules, that contain insect repellent, which are then imparted onto a material to provide long-term repellency with improved water resistance. For example, microcapsules composed of picaridin encapsulated with commercial antibacterial and antifungal microbicide polymer demonstrated significant stability in water and maintained efficacious levels of insect repellency when adsorbed onto nylon-cotton blended fabric.\textsuperscript{12} Nanospheres containing DEET fabricated from miniemulsion polymerization resulted in sustained and temperature-dependent release kinetics.\textsuperscript{13} Furthermore, covalent attachment of DEET to nylon 6 via dye modification demonstrated some insect repellent activity, though chemical modification of DEET reduced efficacy in some cases.\textsuperscript{14} While each of these approaches were effective, a material (ie, fiber) with insect repellent incorporated directly into it at the manufacturing stage would reduce the complexity of many of the coating and particle impregnation methods. 

Electrospinning is a facile method for the fabrication of microscale and nanoscale polymer fibers.\textsuperscript{15} Recently, electrospinning has shown broad capability to generate a variety of polymer fibers of single and composite composition.\textsuperscript{16-18} Electrospun polyacetic acid fibers containing DEET at concentrations exceeding 50 wt% demonstrated uniform fiber morphology and delayed evaporation of DEET as compared to the neat repellent.\textsuperscript{19,20} Furthermore, electrospun pyromellitic dianhydride-cyclodextrin-based fibers were loaded with DEET and shown to maintain fiber morphology, as well as provide increased release times.\textsuperscript{21} Interestingly, coaxial electrospinning provides yet another layer of control,\textsuperscript{22} where fibers with core-sheath morphology are fabricated to contain different compositions in the center of a polymer microfiber/nanofiber, including liquids\textsuperscript{23-25} and bioactive compounds.\textsuperscript{26} Coaxial electrospinning is a convenient and inexpensive method to control morphology and composition, the designs of which can be applied to large-scale fabrication techniques, such as melt extrusion or spinning, for scale-up. Recently, melt spinning was recently used to fabricate bicomponent fibers composed of a DEET and poly(ethylene-co-vinyl acetate) core surrounding by a HDPE sheath that demonstrated long-term efficacy following numerous cold water washes.\textsuperscript{27} Such fibers have not yet been demonstrated using picaridin with traditional textile relevant polymers.

Compared to a monofilament construction, the sheath component of a coaxial fiber would aid in protecting additives in the core for more durable fabrics and act as a diffusion barrier for extended release applications. The sheath material offers the opportunity to tune diffusion rates based on composition, and afford additional control through the modulation of thickness. In this work, picaridin was incorporated into nylon-6,6 nanofibers for the first time via monofilament and coaxial electrospinning. The effects of fiber composition on fiber morphology and release kinetics on monofilament fibers were investigated. Coaxial fibers composed of picaridin loaded nylon core surrounded by an unloaded nylon sheath were fabricated and demonstrated altered release kinetics. Despite the many benefits of picaridin over DEET, including lower vapor pressure, decreased skin sensitivity, and increased fabric resistance, there have been no studies to date on the effects of picaridin loading in fibers through electrospinning and its effects on morphology, structure, and release. This represents a facile method for generating defect-free, insect repellent fibers composed of a textile relevant polymer that can be tuned through traditional electrospinning methods or applied to conventional fiber fabrication methods.

\section{EXPERIMENTAL}

\subsection{Materials}

Pelletized nylon-6,6 was purchased from Sigma-Aldrich (St. Louis, Missouri), while formic acid (88\%) and picaridin (98\%) were purchased from Fisher Scientific and Combi-Blocks, respectively, and used without further purification.

\subsection{Electrospinning}

All electrospun nanofibers were prepared from homogenous solutions with formic acid as solvent and a nylon-6,6 concentration of 12.5 wt\%. In the case of nylon/picaridin (NP) composite fibers, a predetermined amount of picaridin was incorporated into the nylon-6,6 solutions to achieve nominal solution concentrations of 10, 30, and 50 wt\% repellent with respect to nylon-6,6, solids content, designated as NP10, NP30, and NP50, respectively. All solutions were prepared using a FlackTek speedmixer at a spin rate of 3000 rpm until a clear, homogeneous solution was observed.

\subsection{Monofilament electrospinning}

Electrospinning was performed on a custom-built platform equipped with a syringe pump (New Era Pump Systems) containing a filled 12 mL syringe attached to a 22 G needle (D = 0.020 in). Fibers were spun at 15 kV onto a grounded plate at a constant working distance of 10 cm and a flow rate of 15 \muL/min.

\subsection{Coaxial electrospinning}

The same procedure was used for coaxial spinning as for monofilament spinning, however, a coaxial needle (Rame Hart, Succasunna, NJ, inner needle i.d./o.d. = 0.411/0.711 mm, outer needle i.d./o. d. = 2.16/2.77 mm) was utilized where the outer needle solution was a pure (no repellent) nylon-6,6 solution (12.5\% in formic acid) and the inner needle solution was a NP50 solution. To alter the fiber composition, the inner needle flow rate was systematically varied and set at
1.5, 10, and 15 μL/min (15-1, 15-5, 15-10, 15-15, respectively), while the outer needle flow rate was held constant at 15 μL/min for all experiments. For both monofilament and coaxial experiments, electrospun nanofibers were allowed to dry at ambient conditions for 24 hours to ensure any residual solvent was removed.

2.5 Scanning electron microscopy

Images of nanofiber morphology were obtained by scanning electron microscopy (SEM) on a JEOL JSM-7600F field emission SEM (Peabody, Massachusetts) at an operating voltage of 5 kV. Samples were sputter coated with least 3 nm of gold prior to SEM analysis using a Cressington 108 auto sputter coater equipped with a MTM20 thickness controller. Fiber diameters were measured from SEM images using ImageJ software (n ≥ 50). One-way analysis of variance and Tukey post hoc analysis were performed using Origin software.

2.6 Thermal analysis

Analysis of fiber composition and release kinetics were characterized by thermogravimetric analysis (TGA) on a TA Instruments Discovery TGA using platinum pans. Heating ramps were performed at a heating rate of 10°C/min to 600°C. Isothermal measurements were performed in nitrogen atmosphere at 60°C, 80°C, and 100°C for 5 hours. Glass transition temperature (Tg) and thermal behavior were determined on a TA Instruments Discovery differential scanning calorimeter. Temperature ramps were performed from −50°C to 300°C at a rate of 10°C/min.

2.7 Fourier transform infrared spectroscopy

Structural characterization of electrospun nanofibers was investigated through attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were using a Thermo Scientific Nicolet i550-FTIR spectrometer equipped with an i550 ATR attachment and Ge crystal. Background and sample spectra consisted of 128 scans averaged together with 4 cm⁻¹ resolution at a scanner velocity of 10 kHz.

3 RESULTS AND DISCUSSION

Incorporation of the liquid repellent picaridin into solutions of nylon-6,6 (structures shown in Figure 1) in formic acid is expected to behave as a nonvolatile diluent, due to the high boiling point (b.p. = 296°C), homogeneously distributed throughout the fiber matrix during the electrospinning process, resulting in a composition-dependent fiber morphology. After confirmation that NP solutions were miscible over the composition range of interest, fiber morphology was analyzed.

3.1 Monofilament fiber morphology and composition

The effect of repellent content on fiber morphology was investigated with SEM. Representative scanning SEM images, in Figure 2, confirmed that all NP composite fibers were free of defects (eg, globules, ill-defined shape, etc.) and able to be electrospun at all repellent compositions. Unloaded nylon fibers exhibited average fiber diameters of 279 ± 76 nm. The morphology and size of nanofibers was largely unaffected by incorporation of picaridin even at extremely high (ie, 50 wt%) loadings (Figure 3). While fibers containing >50 wt% repellent have been fabricated previously, higher loadings can result in fibers with more defects due to unfavorable microstructure development and phase behavior unacceptable for development of durable fabrics and textiles, resulting in an investigation limited to the above compositions. This result was likely because the picaridin loading had minimal impact on the initial electrospinning polymer solution viscosity and dielectric properties, despite the significant weight contribution of picaridin to fibers after electrospinning. Importantly, picaridin loading did not have negative effects on morphology and size, thus potential development and use of such fibers for repellent textiles are not limited by picaridin loading levels.

The overall composition of electrospun nanofibers were evaluated using TGA. First, TGA ramps were performed to elucidate the overall repellent composition of each of the fibers. Figure 4 shows TGA profiles for each of the NP composite fibers, where the weight loss of at temperatures less than 350°C was attributed to loss of picaridin. A TGA ramp of pure picaridin is included for comparison. Without picaridin, nylon 6,6 did not exhibit weight loss below ~350°C, indicating there was no residual formic acid in the monofilament fibers. Correspondingly, all NP composites also lost all formic acid during electrospinning, as each had only one weight loss step less than 350°C from picaridin. In each case, the experimentally determined picaridin loading was slightly less than the nominal solution concentration used during spinning, indicating that most of the picaridin loading was maintained during the electrospinning process. Discrepancy in these two values can be explained by the low, but nonnegligible vapor pressure of picaridin (~3.3 × 10⁻² Pa) at ambient conditions, that resulted in a portion of the liquid repellent being lost to evaporation during the spinning process.

The effect of picaridin loading concentration on long-term release capability of electrospun NP fibers was evaluated by measuring picaridin release at several elevated temperatures, from which ambient performance can be extrapolated. Specifically, isothermal TGA experiments were performed for each of the fibers at 60°C, 80°C, and 100°C to monitor the diffusion of picaridin from the fibers over time.
Expectedly, the release rate of all samples increased with increasing temperature and increasing picaridin loading (Figure 5A-C). Interestingly, none of the samples released all of the picaridin (noted by dashed horizontal line in Figure 5) after 300 minutes at 100°C, demonstrating significant stability of the NP fibers as well as potential for long-term release capability at lower temperatures. Indeed, all samples continued to release picaridin at the maximum time measured, 300 minutes, even at 100°C. Comparison of NP composites at 60°C, 80°C, and 100°C (Figure 5D-F) demonstrated the effect of fiber composition at constant temperature on release behavior. In all cases, release profiles demonstrated exponential decay in weight retention, \( W_t \), which corresponded to a first order loss of repellent with time that can be further modeled by a simple function of the form

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W_t = W_0 \left( \exp \left( -\frac{t}{\tau} \right) \right) + 1
\]

where \( t \) is the time in minutes, \( W_0 \) is the initial weight, and \( \tau \) is a time constant related to diffusion of picaridin through the electrospun...
nanofibers. Figure 6 depicts the time constant, $\tau$, as a function of temperature for each of the NP composites. In general, extrapolation of time constants across the temperature range demonstrates linear agreement for each sample, except for NP50 at low (60°C) temperatures. This outlier was attributed to several underlying mechanisms that warrant further discussion. Since the fiber diameters for all fibers are statistically similar, there was no surface area effect difference between the samples. Therefore, differences in release profiles were likely due to differing concentration gradients resulting from increased picaridin loading.

The inverse lifetime ($1/\tau$) was fit to an Arrhenius plot (Figure 6, right), from which the activation energy of insect repellent release for each NP composite was calculated from the relationship:
where $E_a$ is the activation energy and $R$ is the universal gas constant (8.314 J/k-mol). The activation energies for all NP composites fall within the range of 37 to 60 kJ/mol. NP10 and NP30 exhibited similar activation energies. NP50 demonstrated slightly higher activation energy at 60 ± 8 kJ/mol, which was attributed to the effect of the 60°C lifetime value on the slope of the NP50 plot. Using the calculated activation energy, the behavior of each composite at ambient temperature, 20°C, was extrapolated and resulted in half-lives ($t_{1/2}$) for release of 13.6, 13.0, and 122.7 hours for NP10, NP30, and NP50, respectively.

In the case of each NP composite fiber, a simple assumption is made that the liquid repellent is homogenously dispersed/incorporated into the nylon matrix resulting in a uniform composition throughout. At relatively low loadings (ie, NP10) it is presumed that this to be a good assumption. However, because picaridin and nylon-6,6 are not miscible, phase separation is expected to occur. At extremely high loadings of repellent (ie, NP50), substantially more phase separation is expected to occur, due to physical confinement, resulting in a nonuniform dispersion of repellent within the polymer matrix. It is therefore anticipated that electrospinning results in a significantly higher repellent composition at the surface of the fiber compared to NP10 or NP30. Additionally, this repellent will inherently behave as a volatile, small-molecule diluent. Consequently, the repellent closest to the surface will diffuse out of the matrix very quickly leaving behind a glassy surface that becomes much more difficult for the picaridin to diffuse through at temperatures below the glass transition temperature of the matrix, resulting in very long repellent lifetimes.

### 3.2 ATR-IR analysis

The structural composition of the NP fibers was evaluated with ATR-IR. Figure 7 shows overlay of NP composite spectra as compared to pure nylon-6,6 and picaridin. Neat picaridin exhibited characteristic broad absorbance at 3434 cm$^{-1}$ from $\nu$(OH), sharp peaks at 2934 and 2866 cm$^{-1}$ corresponding asymmetric and symmetric CH$_2$ ($\nu_{as}$(CH$_2$)), respectively, a shoulder at 1690 cm$^{-1}$ due carbamate carbonyl stretching ($\nu$(C=O)), and a sharp peak at 1659 cm$^{-1}$ from hydrogen bonded carbamate carbonyl stretch($\nu_{s}$(C=O)). Neat nylon-6,6 demonstrated characteristic modes at 3300 cm$^{-1}$ ($\nu$(NH)), 3078 cm$^{-1}$ ($\nu$(HN-C=O)), 2932 and 2861 cm$^{-1}$ corresponding asymmetric ($\nu_{as}$(CH$_2$)) and symmetric CH$_2$ ($\nu_{s}$(CH$_2$)), respectively, 1636 cm$^{-1}$ from amide I carbonyl ($\nu$(C=O)), 1536 cm$^{-1}$ from amide II band ($\nu$(HN-C=O)), and 1275 cm$^{-1}$ attributed to the amide III band. Many of the strong absorbance bands of picaridin overlapped those of nylon-6,6 due to similarity in shared functional groups (amide/carbamate and alkyl moieties, Figure 1). In fact, the NP composites fibers exhibited very similar absorbance to neat nylon-6,6 across most of the IR region, even at the highest (NP50) loading levels. The NH (3300 cm$^{-1}$) and CH$_2$ (2800-3000 cm$^{-1}$) regions were largely unaffected by picaridin loading. Surprisingly, there was no shift in the nylon amide I carbonyl peak upon loading with picaridin, despite the carbamate carbonyl of picaridin absorbing at 1660 cm$^{-1}$ compared to the amide carbonyl of nylon-6,6 at 1636 cm$^{-1}$. Increased picaridin loading was confirmed by the increased intensity of several bands at 1690 cm$^{-1}$ ($\nu$(C=O)), 1423 cm$^{-1}$ ($\delta$(CH$_2$)), 1262 cm$^{-1}$ ($\nu$(C-N)), and 1172 cm$^{-1}$ ($\nu$(C=O)), all of which did not shift relative to neat picaridin. Thus, not only did the increase in these peaks confirm picaridin loading in the nylon fibers, but their lack of shift from neat picaridin also indicated that there were minimal picaridin-nylon
intermolecular interactions. Interestingly, the NP composites exhibited a new peak in the carbonyl region at 1726 cm\(^{-1}\) that was attributed to small amounts of residual formic acid that remained due to stabilizing interactions with picaridin since the peak was not present in neat nylon nor picaridin (Figure 7, right). Taken together, these results suggest that the majority of picaridin was physically entrapped within the nylon matrix. As such, release of picaridin from the monofilament nylon fibers would be expected to be dependent on diffusion of the picaridin insect repellent through the solid polymer matrix, relatively independent of intermolecular interactions.

3.3 Coaxial fiber morphology and composition

In an effort to impart an additional level of control over release kinetics and provide a protective barrier to water exposure, coaxial fibers composed of a picaridin loaded nylon core and an unloaded nylon sheath were fabricated via coaxial electrospinning, utilizing a method adapted from a previous study whereby the flow rates of the core and sheath solutions were manipulated to control fiber composition.\(^{28}\) Specifically, the amount of picaridin loading in the core was controlled by modifying the core solution flow rate (5, 10, and 15 \(\mu\)L/min), which was a picaridin/nylon solution. SEM was used to visualize the effect of coaxial electrospinning and picaridin loading in the core on fiber morphology (Figure 8). Fibers were formed in all cases, though a noticeable increase in defects (i.e., beads) was observed, especially at high core flow rates. This increase in defects is most likely due to the total mass flow exiting the needle tip to be greater than the optimal flow rate that has been shown to produce beaded fibers from reduced charge density.\(^{29}\) The fiber diameters of coaxial fibers were similar to those of the monofilament fibers in the range of 230 to 270 nm (Figure 3). Furthermore, average coaxial fiber diameter was also unaffected by core flow rate. Therefore, all fiber samples exhibited comparable surface area to volume ratios such that differences in release rate were attributed to loading composition and morphology (monofilament vs coaxial).

Repellent composition of the coaxial fibers was determined by TGA. Figure 9 shows TGA heating ramps profiles for all coaxial samples. The first noticeable difference between the coaxial and monofilament profiles is the presence of two regions of mass loss, at \(~150^\circ\text{C}\) and \(~200^\circ\text{C}\). Additionally, in the case of the coaxial nylon-6,6 control, mass loss was also observed at \(~200^\circ\text{C}\) that was not observed in the case of the monofilament control (Figure S1). As such, this mass loss was attributed to trapped residual solvent (formic acid) in the core of the hybrid coaxial nylon structure, suggesting that the mass loss at
4 | CONCLUSION

Repellent nanofibers composed of picaridin in nylon-6,6 were successfully developed. A comparison of fiber morphology on release behavior was performed between monofilament and coaxial fibers. Monofilament composites with varying repellent concentrations were prepared and release rates were tuned and characterized via isothermal TGA. Expectedly, the release rate of all samples increased with increasing core flow rate, demonstrating the ability to tune fiber composition in a simple manner. Indeed, the approximate nominal wt% loadings of the coaxial fibers were 3.5, 5.0, and 10.8 wt% for the 15 to 5, 15 to 10, and 15 to 15 coaxial fibers, respectively. Notably, the 15 to 15 coaxial fibers were comparable in loading concentration to the NP10 monofilament fibers as both were approximately 10 wt% picaridin.

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REFERENCES


**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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