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Controllable and Switchable Drug Delivery of Ibuprofen from Temperature Responsive Composite Nanofibers

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Controllable and switchable drug delivery of ibuprofen from temperature responsive composite nanofibers

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Abstract

Composited electrospun nanofibers made of temperature-responsive poly(N-isopropylacrylamide) (pNIPAM) and biodegradable poly (ε-caprolactone) (PCL) can be utilized for 'on-demand' and controlled drug release of ibuprofen without burst effect for potential pharmaceutical applications. Three types of nanofibers, PCL, pNIPAM and pNIPAM/PCL composite NFs containing ibuprofen were fabricated using electrospinning techniques. Ibuprofen release rates from PCL NFs are not affected by the temperature in the range of 22–34°C (less than 10%). In contrast, the ibuprofen release rates from pNIPAM NFs are very sensitive to the change in temperature, which is five times higher at 22°C compared to 34°C. However, there is a serious burst effect at 22°C. Compared to other two types of NFs, pNIPAM/PCL composite NFs prepared demonstrated a variable and controlled release at both room and higher temperature, due to the extra protection from the hydrophobic poly (ε-caprolactone). The rate at 22°C is 75% faster compared to that at 34°C. This kind of composite design can provide a novel approach to suppress the burst effect in drug delivery systems for potential pharmaceutical applications.

Keywords: Poly (ε-caprolactone); Poly(N-isopropylacrylamide); Nanofibers; Ibuprofen; Controlled release; Temperature-responsive

1 Background

Currently, drug delivery systems are playing an important role in the fields of medical and pharmaceutical sciences [1]. A sustained and controlled release of drug molecules is critically important to tissue engineering and effective treatment of many diseases, ranging from arthritis to cancer therapies [2,3]. In the past decade, advanced nanotechnology and nanoscience have been extensively applied to the fabrication of smart materials which can controllably release drug molecules [4-7]. Despite the positive aspects of using nanomedicine there are still quite a few challenges to overcome. A common problem in drug delivery system is known as burst effect, which is most likely due to the rapid release of surface-associated drug molecules [8]. Another challenge is to realize a programmable drug delivery with variable dosing rates [9].

Modern electrospinning technology allows for drug delivery to be well controlled by tuning spinning parameters and materials. The cost, diameter, composition and structure of electrospun nanofibers can be facilely varied to regulate the drug delivery rates and kinetics. Poly (ε-caprolactone) (PCL) is one of those biocompatible and biodegradable polymers approved by US Food and Drug Administration (FDA) for use in many biomedical devices [10]. PCL has been electrospun into nanofibers for tissue engineering and drug delivery applications due to its high porosity, interconnected pores and high surface area-to-volume ratio [10,11]. However, dosing rates can't be varied under external stimulus. Poly(N-isopropylacrylamide) (pNIPAM) is a quite interesting biocompatible thermo-responsive polymer [12]. When heated above 32°C (its lower critical solution temperature, LCST), pNIPAM undergoes a reversible phase transition from hydrophilic to hydrophobic, losing ~90% of its volume, resulting in the change of drug release rates [13]. Topical administration of levothyroxine using poly vinyl alcohol (PVA) and pNIPAM composite nanofibers were investigated by Azarbayjani

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et al. But it was found that there were serious burst effects at both 25°C and 37°C due to the high water permeability of hydrophilic PVA [14]. Electrospun nanofibers transdermal patches showed great capability for wound healing because they can efficiently absorb exudates due to extremely large surface area. [15,16] Most recently, antibiotic ciprofloxacin loaded hydrophilic biodegradable poly vinyl alcohol electrospun nanofibers have been successfully applied to in vivo wound healing treatment to prevent infections [17].

In this report, electrospun nanofibers made of temperature responsive pNIPAM and hydrophobic PCL polymers were used for controllable and variable ibuprofen (IP) release at both room temperature (22°C) and the temperature above its lower critical solution temperature (LCST) without any burst effects. These nanofibers can

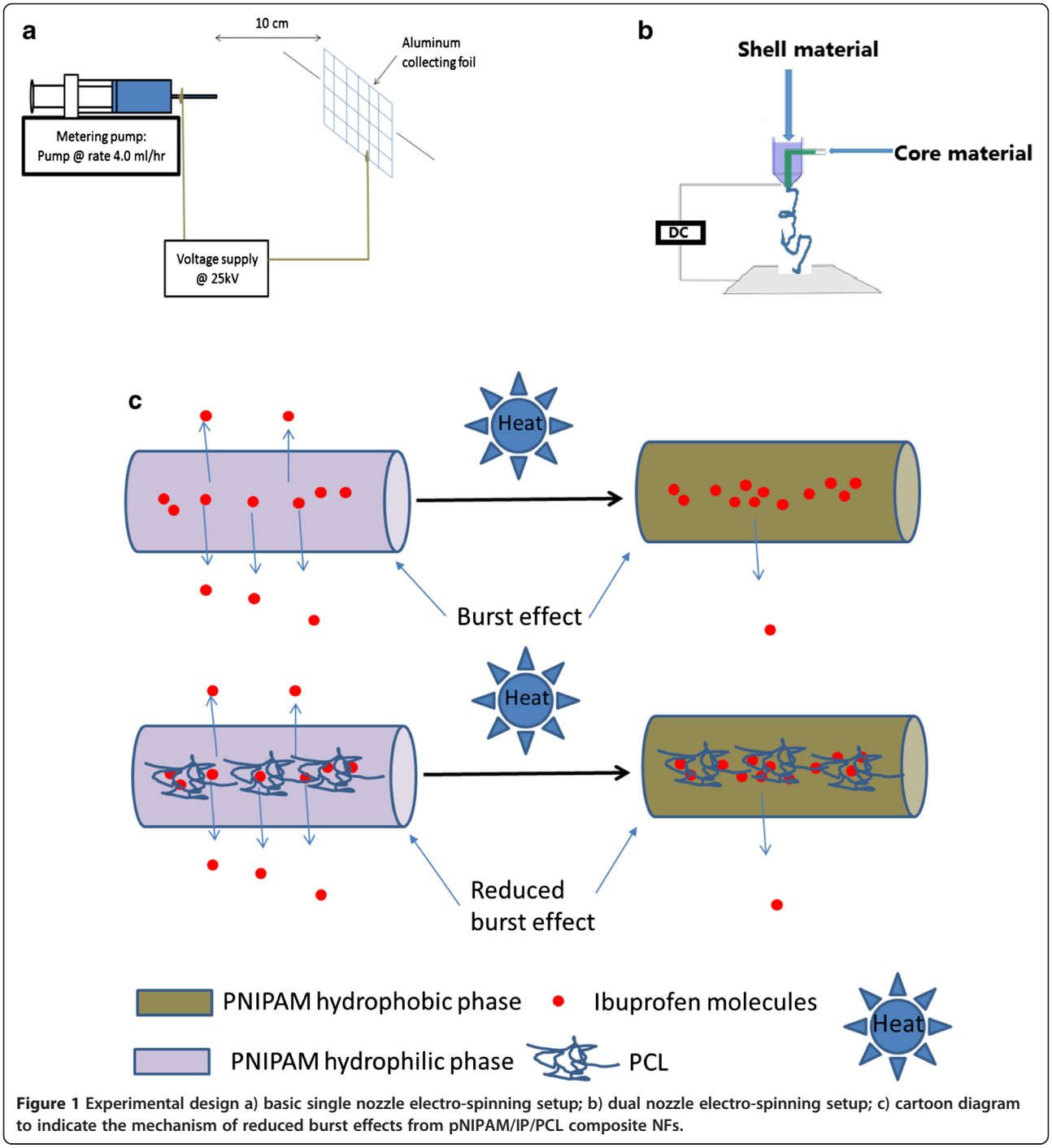

Figure 1 Experimental design a) basic single nozzle electro-spinning setup; b) dual nozzle electro-spinning setup; c) cartoon diagram to indicate the mechanism of reduced burst effects from pNIPAM/IP/PCL composite NFs.

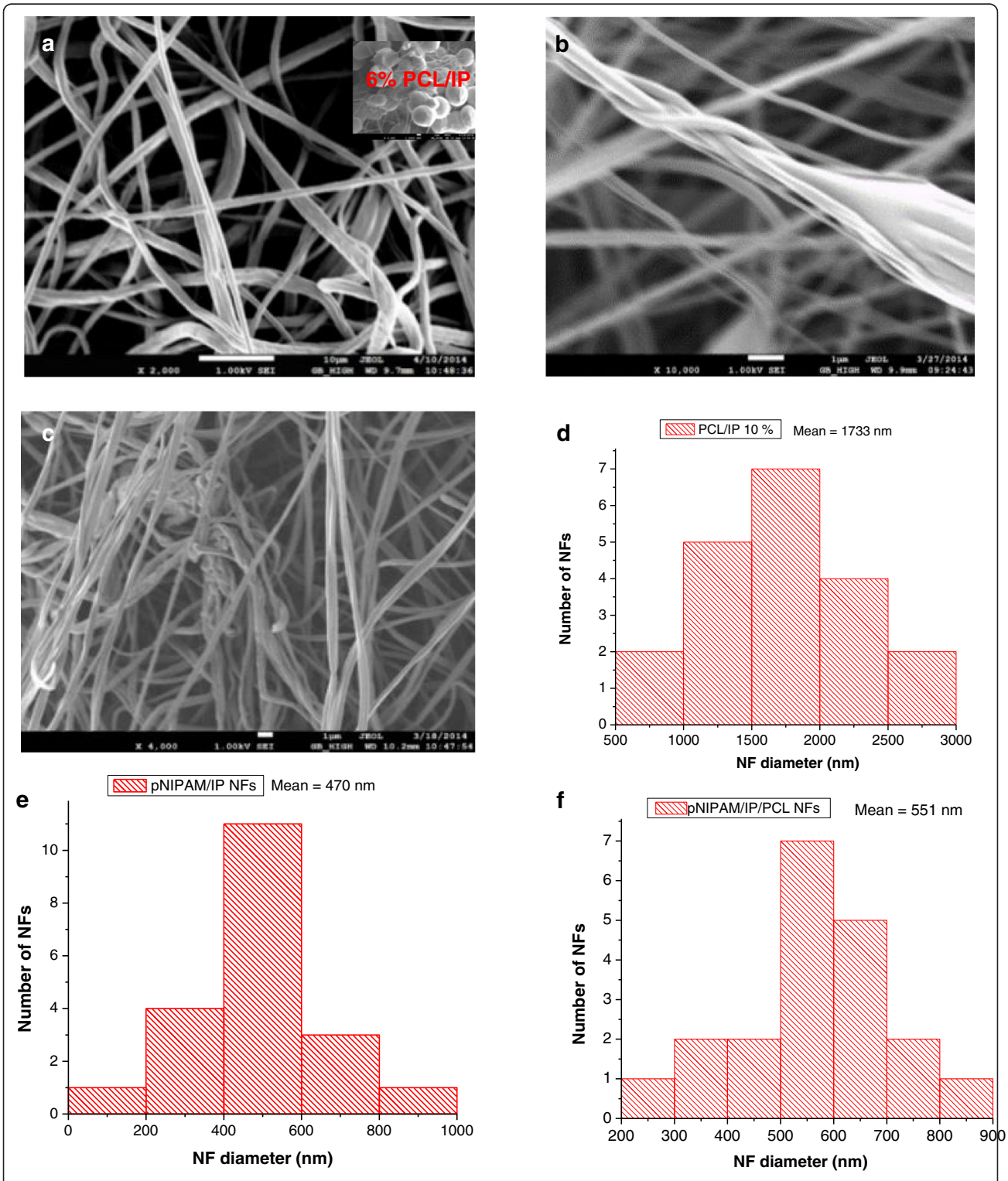

Figure 2 Scanning electron spectroscopy images of three types of NFs, a) PCL/IP, b) pNIPAM/IP and c) pNIPAM/IP/PCL composite NFs and their corresponding histograms in NF diameter distribution d), e) and f), respectively. Scale bars for **(a)**, **(b)** and **(c)** are 10, 1 and 1 μm, respectively.

be applied to transdermal drug delivery that can significantly enhance the efficacy of drug addiction and abuse treatments [9].

2 Methods

2.1 Materials

PCL with an average Mn of 45,000 and pNIPAM with an average Mn of 19,000-30,000 were purchased from Sigma-Aldrich. Ibuprofen with a purity >99.0% was obtained from ACROS Organic. Ethanol and acetone with purity higher than 99.5% were purchased from EMD Millipore. Acetonitrile used for HPLC analysis was purchased from EMD Millipore also.

2.2 Fabrication of nanofibers

Three types of nanofibers (NFs) were fabricated using a homebuilt electrospinning setup, including PCL/IP, pNIPAM/IP and pNIPAM/IP/PCL composite NFs. The schematic of electrospinning setup, working parameters and detailed experimental conditions are shown in Figure 1. The electrospinning working parameters were as follows: applied voltage was direct current (DC) 25 kV (Spellman P/N230-30R); distance between the syringe needle (16 gauge, Air-Tite Products Co.) containing the solution and the grounding collector (aluminum foil) was 10 cm; and pumping rate of syringe was 4 ml/hr. The syringe pump was purchased from New Era Pump Systems Inc. (NE-1000). *Fabrication of PCL/IP NFs:* First, 50 mg IP and 1.0 g PCL pellets were dissolved in 10 mL acetone under magnetic stirring and sonication. Then the solution was electrospun into PCL/IP NFs using a single nozzle spinet. *Fabrication of pNIPAM/IP NFs*: 50 mg IP and 1.0 g pNIPAM powders were dissolved in 5.0 mL ethanol under magnetic stirring. Then the solution was used to fabricate pNIPAM/IP NFs using a single nozzle spinet. *Fabrication of pNIPAM/IP/PCL composite NFs:* 50 mg IP and 1.0 g pNIPAM powders were dissolved in 5.0 mL ethanol under magnetic stirring and used as the solution for the core needle. 0.6 g PCL pellets were dissolved in 10 mL acetone under magnetic stirring and sonication, and used as the solution for the shell needle. A double spinet was used for the electrospinning, whose inner and outer needle sizes were 21 and 16 gauges, respectively. The flow rates of both core and shell needles were 4 mL hr^{-1}.

2.3 Characterization of nanofibers

The prepared samples were characterized using a Field Emission Electron Microscopy (JEOL JSM-7600 F) at Georgia Southern University for morphology examinations. Fourier-Transform Infrared (FTIR) spectra of nanofiber samples were recorded in the attenuated total reflection (ATR) mode using an IR spectrophotometer (Thermo-Nicolet AVATAR 370 FT-IR Spectrometer) in the range of 4000 to 650 cm^{-1} at Georgia Southern University.

2.4 Drug diffusion studies

All ibuprofen studies involving these three types of NFs were carried out using a 5 mL PermeGear Franz cell with a 10 mm diameter orifice for sampling. ~20 ± 1 mg NFs were wetted and suspended in the receptor chamber containing 4.0 mL of deionized water and a magnetic stirring bar. It was calculated that there were 4.8, 4.8 and 3.7 μmol of ibuprofen in PCL/IP, pNIPAM/IP and pNIPAM/IP/PCL fibers, respectively. 1 mL solution was pipetted from the receiver chamber per hour and stored into 1.8 mL amber glass vials for HPLC analysis. The chamber was back-filled with 1.0 mL deionized water after each sampling. All drug release profiles were averaged from triple measurements.

2.5 HPLC measurements and data analysis

All ibuprofen samples were analyzed by a Shimadzu LCAT High Performance Liquid Chromatography (HPLC) consisting of a SIL-20AHT autosampler, a LC-20AT HPLC pump, a SPD-20A dual UV/Vis absorbance detector set at

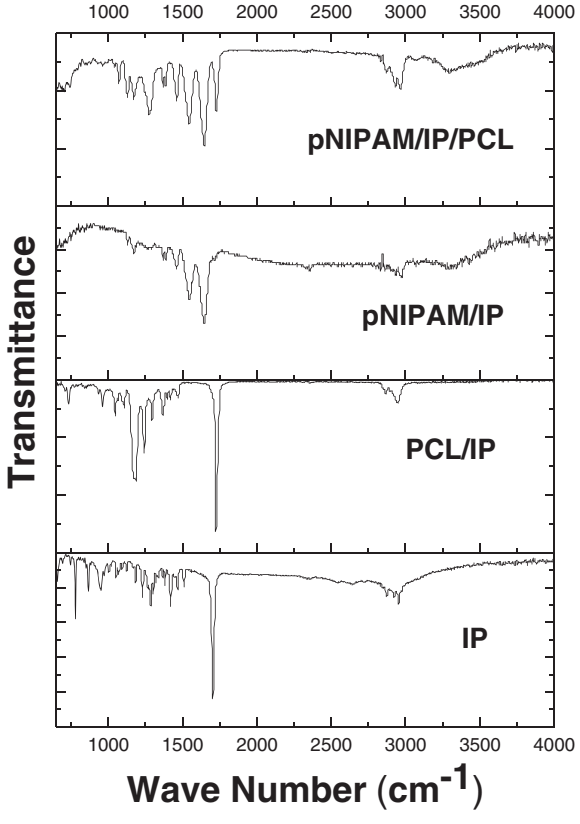

Figure 3 Frourier transform Infrared spectra of IP and three types of electrospun nanofibers, ase well as pure ibuprofen.

a wavelength of 254 nm and utilizing LabSolutions software. Thermo Scientific HyPURITY C18 reversed-phase 5 μm column (250 mm × 4 mm; L × I.D.) was used for the separation. The mobile phase consisted of 0.1 wt% H_3PO_4 aqueous solution:acetonitrile (55:45) and flow rate of 1.0 mL/min. Calibration plots were prepared using IP standards with concentrations over a range of 20–100 μg/ml. The correlation coefficient (r^2) obtained was ≥0.99 for standard curves. The cumulative quantity of drug collected in the receiver compartment was plotted as a function of time. This method was adapted from a literature reported method [18]. The lower limit of quantification (LLOQ) was 2 μg/ml.

3 Results and discussion

The average diameter of PCL/IP NFs was ~1.7 μm with a wide distribution from 500 nm to 3 μm as shown in Figure 2a and d. If the concentration of PCL solution was reduced from 10% to 6% (w/v), the diameters of PCL/ibuprofen fibers can be significantly reduced to below 300 nm on average. But there were both fibers and beads, thus making the interpretation of diffusion data very difficult. Figure 2b and e shows that the diameters of pNIPAM/IP nanofibers were in the range of 100–900 nm with an average of 470 nm. Compared to PCL NFs, the standard deviation in the diameters for pNIPAM NFs was much smaller. In the case of pNIPAM/IP/PCL composite nanofibers, the average diameter and diameter distribution were quite similar to those of pure pNIPAM NFs (Figure 2c and f). Noteworthy, no apparent drug particles were observed on the surface of these NFs, thus benefiting a reduced burst effect associated with surface drug molecules.

These NFs were further characterized using Fourier transform infrared (FTIR) spectroscopy (Figure 3). The PCL/IP FTIR spectrum shows there are PCL finger prints peaks at 2948 and 1728 and 1190 cm^{-1}, which can be assigned to the asymmetric C-H stretching, carbonyl stretching and C–O stretching, respectively [19]. In the FTIR spectrum of PNIPAM/IP nanofibers, characteristic peaks of pNIPAM located at 1650 and 1550 cm^{-1} can be assigned to amide carbonyl stretching and amide N-H bending, respectively [20]. In the case of pNIPAM/IP/PCL composited NFs, finger prints of both pNIPAM and PCL can be clearly seen at 1190, 1550, 1650, 1728 and 2946 cm^{-1}. The IP peaks can't be clearly observed might be due to its low weight percentage (5 wt%).

The release rates of ibuprofen from three types of NFs were investigated in pH 7.4 deionized water at 22°C and 34°C (Figure 4 and Table 1). It is seen that 1 μmol of

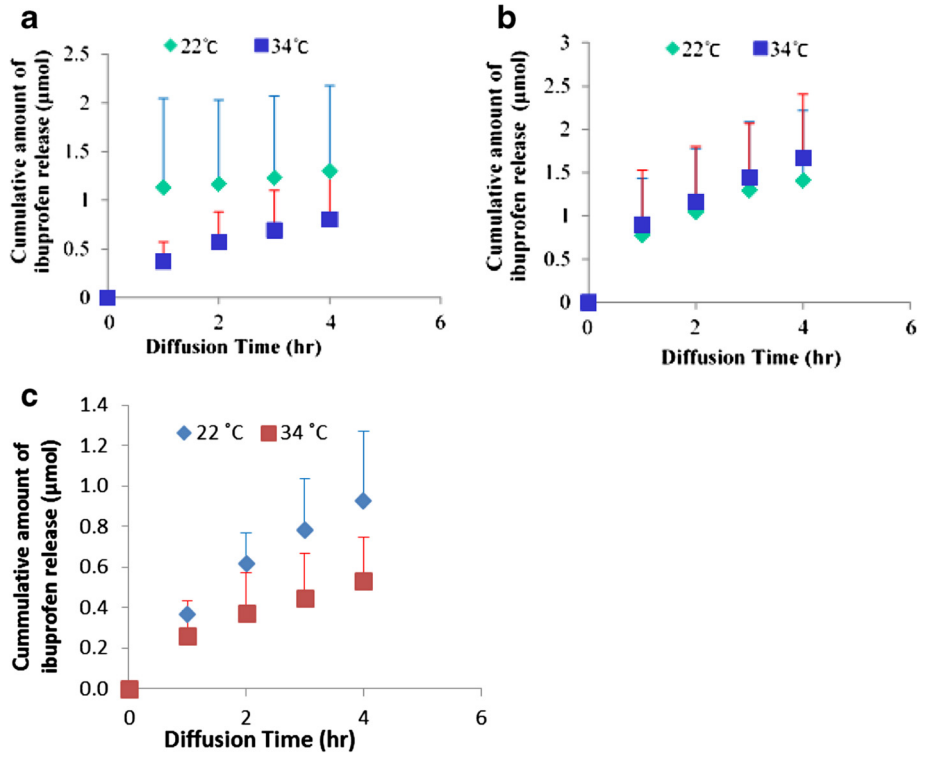

Figure 4 Ibuprofen release profiles from a) pNIPAM NFs containing 50 mg Ibuprofen/g NFs; b) PCL NFs containing 50 mg Ibuprofen/g NFs; c) pNIPAM and PCL composite NFs containing 50 mg Ibuprofen/g pNIPAM NFs. (*standard deviation bars were obtained from the measurements of triple diffusion studies. The level of significance was set at a p value of less than 0.05).

Table 1 Average cumulative amount of IP released from three types of NFs at 22 and 34°C

	Cumulative amount of IP released at 1 hr	Cumulative amount of IP released at 2 hr	Cumulative amount of IP released at 3 hr	Cumulative amount of IP released at 4 hr
pNIPAM 22°C	1.13	1.17	1.23	1.30
pNIPAM 34°C	0.37	0.57	0.69	0.80
PCL 22°C	0.78	1.05	1.30	1.41
PCL 34°C	0.90	1.17	1.44	1.67
pNIPAM/PCL composite NFs 22°C	0.36	0.62	0.78	0.93
pNIPAM/PCL composite NFs 34°C	0.26	0.37	0.45	0.53

ibuprofen was quickly released from pNIPAM/IP NFs in the first one hour at 22°C, and then the rest was released at a much slower rate, 0.05 μmol hr^{-1}. Totally, 24% IP was released in four hours. In contrast, IP was released at a more controllable mode when the temperature was increased to 34°C. The average release rate was ~ 0.2 μmol hr^{-1} and ~ 0.4 μmol IP was released in the first one hour. Only 17% IP was released in 4 hrs. This phenomenon can be explained by the high water solubility of pNIPAM when the temperature was below its LCST (32°C), leading to the fast IP release from the polymeric matrix. However, pNIPAM becomes much hydrophobic when temperature was above its LCST. Thus pNIPAM functions like a drug depot to prohibit the fast release of hydrophobic IP molecules, resulting in the relatively more controllable release mode. For PCL/IP NFs, ~15% IP was released in the first 1 hr at 22°C and 34°C and there was less than 10% change in devliery rates for both temperatures. On average, 34% IP was released in 4 hrs. In the case of composite pNIPAM/IP/PCL NFs, the diffusion rates at both 22°C and 34°C were quite linear and well controlled without burst effects. The controlled release was due to the presence of PCL barrier that can provide extra buffer zone to reduce burst effect, especially at lower temperature (below the LCST of pNIPAM). Compared to the IP release rate at 34°C, the average IP release rate from this composite NF was 75% faster at 22°C. Similiarly, it is because pNIPAM was quite hydrophilic at room temperature. So water molecules can diffuse through the PCL barrier and carry out IP molecules more quickly. At high temperature, both PCL and pNIPAM were hydrophobic, thus leading to a reduced release rate of hydrophobic IP. On average, 13% and 25% IP were released from pNIPAM and PCL composite NFs at 34 and 22°C, respectively.

4 Conclusions

Three types of polymeric nanofibers were fabricated using electrospinning method for drug delivery studies. Temperature has negligible effects on the IP diffusion rates from PCL/IP NFs. For pNIPAM/IP NFs, there is a significant burst effect at 22°C; whereas both diffusion rate and burst effect are dramatically depressed at a higher temperature. For pNIPAM/IP/PCL composite NFs, burst effect was significantly reduced for both 22°C and 34°C. The diffusion rate is higher at 22°C compared to that at 34°C by 75%. It can be naturally envisioned that such kind of controllable and switchable delivery systems could easily find many practical applications in both pharmaceutical and medical sciences.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TT, MH, EB, VP and DP carried out the experiments and were involved in manuscript preparation. JW designed the experiments and prepared the manuscript. All authors participated in the result discussions. All authors read and approved the final manuscript.

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