Poly(*N*-isopropylacrylamide)/polyurethane core–sheath nanofibres by coaxial electrospinning for drug controlled release

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A new type of drug carrier with thermo-sensitivity is reported. The system consisted of poly(*N*-isopropylacrylamide) (PNIPAAm) and polyurethane (PU) and two kinds of polymer were spun into core–sheath nanofibres without bead defects by coaxial electrospinning technique. Poor soluble nifedipine was used as a model drug to evaluate the release behaviour of drug from nanofibre carriers. Results showed that the diameter and diameter distribution of nanofibres varied with the ratios of the outer flow rate to the inner flow rate. PNIPAAm/PU core–sheath electrospun nanofibres maintained the thermo-sensitivity of PNIPAAm and the wettability of the electrospun nanofibres could be adjusted effectively by the change of the temperature. In-vitro release of nifedipine from nanofibre carriers showed that core–sheath electrospun nanofibres as the drug carrier could slow down the release rate of nifedipine compared with that of PNIPAAm/PU composite electrospun nanofibres, and then could effectively achieve the controlled release of nifedipine, avoiding the concentrated release of drug and reduce the toxicity.

1. Introduction: Electrospun nanofibres with finer diameters prepared by electrospinning technique had broad range of applications [1–3]. Much attention has been attracted for such materials in the applications of drug carriers, tissue scafford and templates for producing functional nanoobjects [4–8]. Core–sheath structure electrospun fibres by coaxial electrospinning as drug carriers can further control drug release better and reduce toxicity [9, 10]. The principle of coaxial electrospinning is the same with the single-spinneret electrospinning technique [11, 12]. However, due to the replacement of single needle by coaxial needle, different multi-components core–sheath nanofibres can be fabricated with different diameters and morphology.

Poly(*N*-isopropylacrylamide) (PNIPAAm) core–shell nanoparticles with thermo-sensitivity attracted many researchers and have been studied extensively, especially in biomedicine field [13–16]. However, the fabrication of core–sheath nanofibres from PNIPAAm is scarcely studied [17, 18]. Chen and his coworkers prepared polycaprolactone diol (PCL)/PNIPAAm core–sheath nanofibres by single-spinneret electrospinning technique. Both the differences of solvent parameters and molecular weights of polymers led to the self-assembly of core–sheath nanofibres. The combination of thermo-sensitivity of PNIPAAm and biodegradability of PCL within a core–sheath system would flourish their potential bio-applications [18]. This report provided information for the fabrication of PNIPAAm core–sheath electrospun nanofibres.

In this report, PCL was the raw material to synthesise polyurethane (PU) with good biocompatibility and potential applications in biomedicine [19, 20]. Poly(*N*-isopropylacrylamide)/polyurethane (PNIPAAm/PU) core-sheath electrospun nanofibers were fabricated with PU as the sheath by coaxial electrospinning technology. Core–sheath nanofibres with different diameter were spun through changing the inner and outer flow rates of coaxial needle. Thermo-sensitive behaviour of the PNIPAAm/PU core–sheath electrospun nanofibres would be studied by the contact angle (CA) measurements test. Nifedipine was used as a model drug to study the control function of core–sheath and composite electrospun nanofibres to drug release.

2. Experimental

2.1. Materials: All monomers were used directly without purification. *N*-isopropylacrylamide and PCL ($M_n = 2000$) (TCI, Japan), isophorone diisocyanate (Alfar, USA) were the main ingredients. *N*, *N*, *N*′, *N*′-tetramethylethylenediamine (Shanghai Adamas, China) was used to accelerate reaction, and 1, 4-butanene diol (Shanghai Adamas, China) was used to increase viscosity. PNIPAAm and PU were both synthesised with the same procedures as previously reported [19, 21].

2.2. Preparation of electrospun nanofibres: About 0.2738 g of PNIPAAm and 0.3412 g of PU solid were dissolved in up to 3 ml N, N-dimethylformamide (DMF) and stirred for 4 h at room temperature (22°C). Nifedipine was added in PNIPAAm/DMF solution and the content was 30%.

Fig. 1 showed the electrospinning setup, including power supply providing high-voltage electric field, an aluminium plate collector and two promoting pumps. The promoting pump controlled syringe equipped with PNIPAAm solution and PU solution. The syringe equipped with PNIPAAm solution connected a coaxial needle of the internal diameter of 0.51 mm and the external diameter of 0.82 mm.

The electrospun solution was fed into 5 ml plastic syringes. Electrospinning was carried out according to the following parameters: the flow rate ratio of shell and core solution was 2:1, 3:1 and 4:1, the high voltage and the collected distance were 15 kV and 22 cm. PNIPAAm/PU core–sheath fibre films were obtained on the collector.

2.3. Morphology of electrospun nanofibres measurements: The aluminium plate collected electrospun nanofibres were cut into small pieces, and then coated with gold on the surface of fibre films for 8 min at 45 mA. Images were obtained by a Helios

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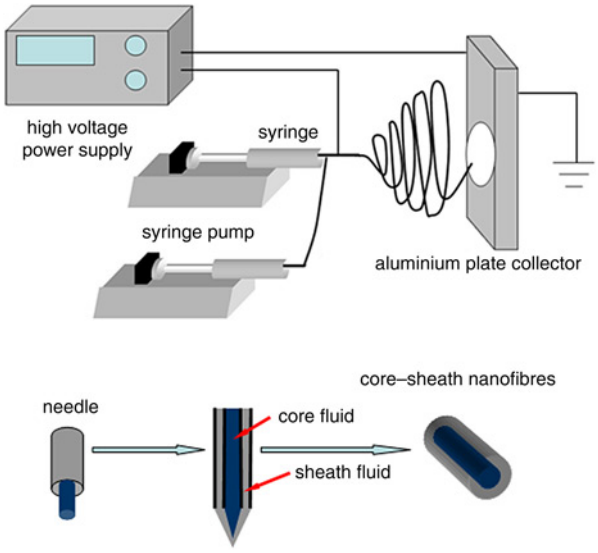

Fig. 1 *Schematic diagram of coaxial electrospinning setup and needle*

Nanolab 600i scanning electron microscopy (SEM) at 20 kV. The electrospun nanofibres were combined into very thin film on the copper grid and loaded into an H-7650 transmission electron microscopy (TEM). Analysis was conducted at voltage 100 kV.

Thermo-sensitivity of electrospun fibre films and in-vitro release of nifedipine from electrospun nanofibres used the same procedures as previously reported [22].

3. Results and discussion

3.1. Morphology of PNIPAAm/PU core–sheath nanofibres: Fig. 2 shows TEM images of PNIPAAm/PU core–sheath nanofibres with different outer and inner flow rate ratios. The outer flow rate was 0.16, 0.25, 0.33 and 0.33 mL/h, and the inner flow rate was 0.08, 0.08, 0.08 and 0.16 mL/h. TEM images showed that middle part presented the darker colour due to existing two components. It can be seen that varying the outer flow rates and keeping inner flow rate constant could change the diameter of core–sheath nanofibres. SEM images would illustrate the trends further.

SEM images of PNIPAAm/PU core–sheath electrospun nanofibres formed under different flow rate ratios can be seen in Fig. 3. Smooth but inhomogeneous finer nanofibres are shown in the images. The diameter of electrospun fibres was calculated using Image J and the reported data was the average values. Figs. 3*a* and *b* show the SEM images of PNIPAAm/PU core–sheath electrospun fibres with the average diameter of 383 ± 34 and of 362 ± 25 nm, respectively. Fig. 3*c* shows the SEM image of PNIPAAm/PU core–sheath fibres with the average diameter of 330 ± 25 nm. When the outer to inner flow rate ratios was 4:1, the uniformity in diameter of nanofibres decreased. The individual nanofibres with bigger diameter of 802 ± 115 nm appeared in Fig. 3*c*. Due to

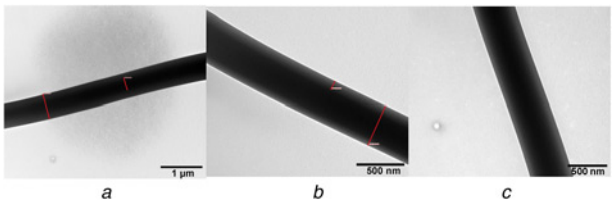

Fig. 2 *TEM images of PNIPAAm/PU core–sheath electrospun fibres with different outer/inner flow rate ratios*
a 2:1
b 3:1
c 4:1

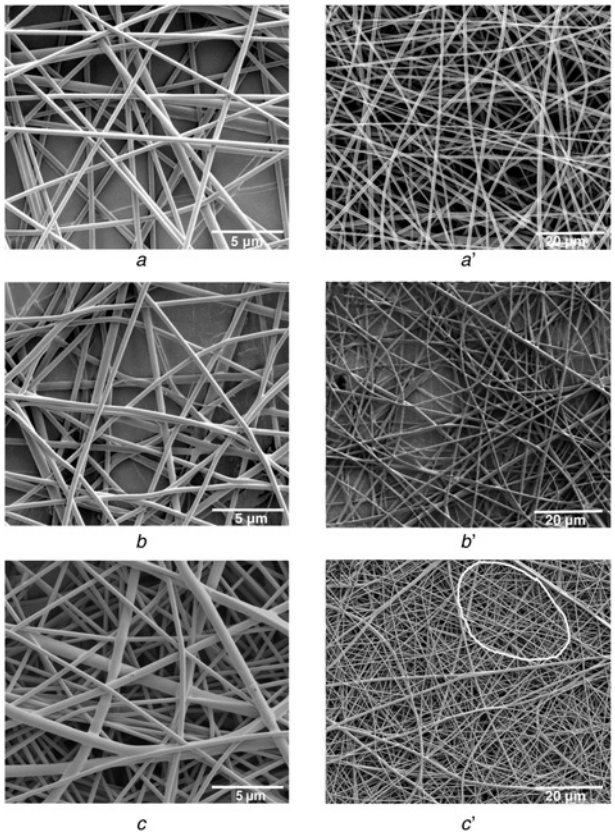

Fig. 3 *SEM images with different magnification of PNIPAAm/PU core–shell nanofibres with different outer to inner flow rate ratios*
a, a′ 2:1
b, b′ 3:1
c, c′ 4:1

the volume of solution increased with the increase of the outer flow rates while unchanged inner flow rates, the diameter of nanofibres increased with the increase of the flow rates. However, if the outer flow rates of solution were too large, the needle would easily be blocked, and thus Taylor cone diverged, so that the diameter distribution of nanofibres became uniform and the average diameter became smaller further.

3.2. Thermo-sensitivity of nanofibres: The change of the sensitivity of the PNIPAAm/PU core–sheath electrospun nanofibres with temperatures was shown in Fig. 4 (curves of CAs at 24 and 45°C within 10 s and water drop photographs at every 1 s). At 24°C, water droplets became flat after 10 s and the curve showed the initial CA values of 127°, and the final CA values of 50° after 10 s. While at 45°C, the CA values were almost constant for the droplets on the surface of nanofibres. The initial CA was 130° and the final CA was 123° after 10 s. These showed that the component of PNIPAAm played the thermo-responsive character within core–sheath nanofibres. Although PNIPAAm existed in the inner layer of core–sheath nanofibres, but below the lower critical solution temperature (LCST) of PNIPAAm (at 24°C), water molecules could pass through the outer layer of PU molecules of PNIPAAm/PU core–sheath nanofibres, and thus the hydrogen bonding that formed between PNIPAAm molecules and water molecules would supply the hydrophilicity to PNIPAAm/PU core–sheath nanofibres. With the increase of temperature, the molecular chains of PNIPAAm shrank so that the nanofibres became more compact, and thus the holes between the nanofibres tend to disappear. PNIPAAm molecules were surrounded by hydrophobic molecules of PU and thus could not form the intermolecular hydrogen bonding with water molecules. Hence,

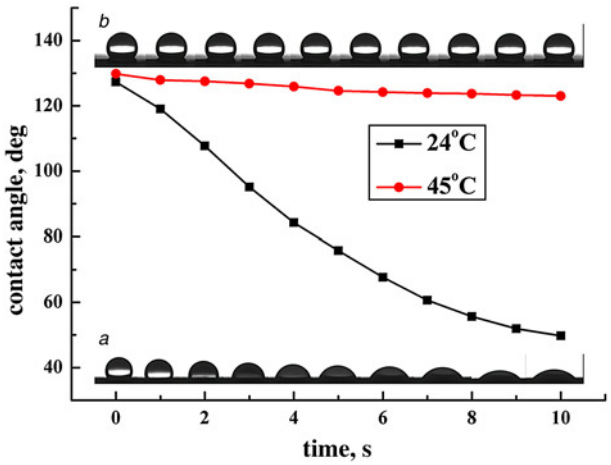

Fig. 4 *Effect of times on the CAs of PNIPAAm/PU core–sheath nanofibres and the shape of water droplet on the surface of fibre films at different temperatures*
a 24°C
b 45°C

above the LCST of PNIPAAm (at 45°C), the shape of water drop on the surface of nanofibres was almost the same with almost the same CA values of 123°. This result showed that, as the inner component of the core–sheath electrospun nanofibres, PNIPAAm could still affect the hydrophilic/hydrophobic properties of PNIPAAm/PU core–sheath nanofibres. That is to say, PNIPAAm/PU core–sheath nanofibres still maintained the thermo-sensitivity of PNIPAAm and appeared obvious hydrophobicity at temperatures above the LCST of PNIPAAm.

Fig. 5 shows that the CA on the surface of electrospun fibre films changed with temperature after 10s. The CA increased gradually with the increase in temperature. When the temperature was 34°C, the CA was close to 90°, whilst at 36°C, the CA on the surface of PNIPAAm/PU core–sheath electrospun nanofibres was equal to 106°. Compared with two curves in Fig. 5, the CA on the surface of PU/PNIPAAm composite electrospun nanofibres was almost equal at 24–30 and 34–36°C. The CAs on the surface of PNIPAAm/PU core–sheath electrospun nanofibres increased gradually at 32–36°C. Therefore, each component existed lonely in PNIPAAm/PU core–sheath structured nanofibres. This structure played their respective component characteristics better. Whereas, the PU and PNIPAAm components were combined together by solution blend in PU/PNIPAAm composite nanofibres. The CA measurement reflected in the functionality of PNIPAAm

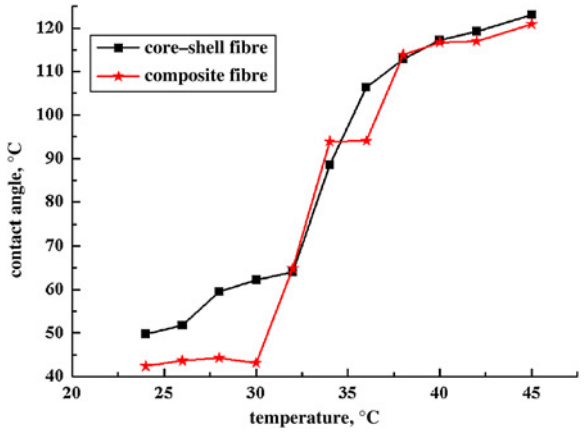

Fig. 5 *Effect of temperature on the CAs of PNIPAAm/PU electrospun fibre films*

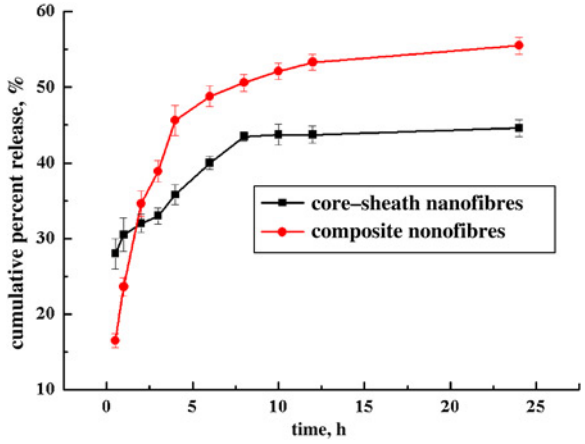

Fig. 6 *Cumulative release curves of nifedipine from PNIPAAm/PU electrospun nanofibres at different times*

component in nanofibres mainly. These results showed that the thermo-sensitivity of PNIPAAm/PU core–sheath nanofibres was higher than that of PU/PNIPAAm composite nanofibres obviously.

3.3. In-vitro release of nifedipine from nanofibres: The core–sheath electrospun nanofibres with the hydrophobic outer layer of PU and the hydrophilic inner layer of PNIPAAm could also act as a carrier for drugs. The release amount curve of nifedipine from PNIPAAm/PU core–sheath electrospun nanofibres and PNIPAAm/PU composite nanofibres (for comparison) was shown in Fig. 6. It can be found, by comparing the shape of the two curves, the release amount of nifedipine from the PNIPAAm/PU composite electrospun nanofibres more quickly increased. After 3 h, the release amount became higher than that from core–sheath electrospun nanofibres and the release amount reached 56% after 24 h.

For the PNIPAAm/PU composite nanofibres, two polymer components could form uniform solution before electrospinning, so the initial release amount of nifedipine from the composite nanofibres was less than that from core–sheath nanofibres. The outer layer of core–sheath nanofibres was PCL-based PU with relative slow degradation rate. Nifedipine within the inner layer need to pass through PU molecule, then diffused into the release medium. Thus, the release amount of nifedipine from PNIPAAm/PU core–sheath nanofibres increased more gradually and remained almost the same after 24 h. Therefore, core–sheath electrospun nanofibres as the carrier of nifedipine could slow down the release rate of nifedipine effectively. Then, the controlled release of nifedipine is achieved, especially for the core–sheath nanofibres with PCL-based PU as sheath.

4. Conclusion: PNIPAAm/PU core–sheath electrospun nanofibres could be fabricated by coaxial electrospinning technology. The appropriate electrospinning parameters were: 12% of solution concentration, 15 kV of voltage, 20 cm of collector distance, 0.16 ml/h of outer flow rate and 0.08 ml/h of inner flow rate. Such electrospun nanofibres maintained the functionality of each component. The surface hydrophobic ability of PNIPAAm/PU core–sheath electrospun nanofibres could be improved with the increasing of temperatures. When the temperature increased from 34 to 45°C, the CA was increased from more than 90° to 123° indicating the improvement of the resistance to water. Compared with PNIPAAm/PU composite nanofibres, core–sheath electrospun nanofibres as the drug carrier of nifedipine could slow down the release rate of nifedipine, and then further achieve the controlled release of nifedipine effectively.

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