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Preparation of ultra-porous UPM/PHBV nanofibres using solvent-etching technology and drug-loading efficiency

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In this study, ultra-porous fibres have been produced by partly washing out poly(3-hydroxybutyrateco-3-hydroxyvalerate) (PHBV) from the heat-crosslinked electrospun unsaturated polyester macromonomers/poly(3-hydroxybutyrateco-3-hydroxyvalerate) (UPM/PHBV) fibrous composite using chloroform. Tetracycline hydrochloride has been used as the module drug to test the drug-loading efficiency of porous fibres. Field emission scanning electron microscope images show that the etched UPM/PHBV fibres have lost the original smooth surface. The result demonstrates that the PHBV is successfully washed by chloroform, but most of UPM is remained because of the heat-crosslinking. Furthermore, with the increase of PHBV ratio in composite fibres, the etched fibres show much rougher surface. The drug absorption behavior also varies with the different PHBV ratios.

Keywords: Drug loading efficiency, Electrospinning, Poly(3-hydroxybutyrateco-3-hydroxyvalerate), Solvent etching, Ultra-porous fibres, Nanofibres, Unsaturated polyester macromonomers

Electrospun polymeric nanofibres and nanofibrous mats show many distinctive properties such as high surface area-to-volume ratio, high porosity, and high absorption[1-3]. The morphology of nanofibres can be adjusted by changing the electrospinning parameters such as initial polymer concentration, solution density, electric potential, perturbation frequency, solvent vapor pressure and additive type. With the development of functional electrospun fibres, many new methods have been applied to change their surface structure, thermal or solvent stability and its mechanical strength properties by surface modification, heat treatment and chemical crosslinking[4-6]. The porous-structure on fibres surface could increase absorption ability to small molecules such as drug or proteins; and further increase fibre area-to-volume ratio. The ultra-porous fibres can be obtained by selectively removing one of components in electrospun nanofibres composite. In general, many methods including selective dissolution, thermal degradation, or photo-degradation can be employed to remove the component[7-9].

In this study, ultra-porous fibres of unsaturated polyester macromonomers (UPM) have been produced by washing out poly(3-hydroxybutyrateco-3-hydroxyvalerate) (PHBV) from the heat-crosslinked electrospun UPM/PHBV fibrous composite using chloroform. UPM has been boasted for extensive use in high performance engineering thermoplastics because of its excellent mechanical, thermal, biocompatibility and chemical properties[10]. After heat-crosslink, the UPM network can resist high temperature and solvent effectively. PHBV has been known as a biodegradable thermoplastic which can be decomposed rapidly in chloroform. Crosslinked UPM and PHBV show significant dissolving ability, and therefore, chloroform has been selected for preparing the ultra-porous fibres by etching PHBV from UPM/PHBV nanofibres composite. Tetracycline hydrochloride (TH) is used as the active pharmaceutical ingredient for testing the adsorption efficiency through dipping the fibrous mats into the TH-contained solutions. The absorption behavior of TH from UPM ultra-porous fibres with various surface conditions is also investigated.

Experimental

Materials

Unsaturated polyester macromonomers (UPM) was synthesized from poly(2-methyl-1,3-propylene adipate), diol terminated (PMPA) with average molecular weight of 2000 and 2-hydroxyethyl methacrylate (HEMA); UPM was purchased from Sigma-Aldrich Co.Ltd (USA). Isophorone diisocyanate (IPDI) and dibutyltin dilaurate (DBTDL) (catalyst) were purchased from Fluka Co. Ltd (USA). Poly(3-hydroxybutyrateco-3-hydroxyvalerate) (PHBV)(Mn 460,000, HV content 3%) was kindly supplied by Ningbo TianAn Co.Ltd (China). Chloroform and benzoyl peroxide (BPO) (initiator) were purchased from Sinopharm Chemical Reagent Co.Ltd. All the chemicals used were of analytical grade and used as such without further purification. The model drug TH was obtained from Sigma Co.Ltd. Phosphate Buffer (PBS) solutions, purchased from

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Pinghu Chemwastry Factory (Zhejiang, China), were applied as dissolution media.

Electrospinning

In order to prepare UPM/PHBV blend solutions, 10 wt% of UPM and 10 wt% of PHBV solutions in chloroform were first prepared and minimum BPO was added into solvent. The mixed ratios were predetermined as UPM: PHBV: BPO =10:1:0.01 to 1:4:0.01(w/w/w). The experimental set-up used for conducting electrospinning included a high voltage power supply (JG50-1 high voltage generator, Shenfa Co. Ltd., Shanghai, China), and a digitally controlled syringe pump (Model 100, KD Scientific). During electrospinning, a positive high voltage of 10 kV was applied at the tip of a syringe needle with an inner diameter of 0.9 mm. The electrospun nanofibres were collected on a piece of aluminum foil placed at a distance of 15 cm below the tip of the syringe needle. The flow rate of electrospun solution was maintained at 1.0 mL/h. All processes of electrospinning were conducted at room temperature. The UPM and PHBV pure nanofibres were also prepared for solvent etching measurement.

Thermal Crosslinking and Solvent Etching

The thermal crosslinking process was carried out by placing the UPM/PHBV nanofibres composite in a vacuum oven at 90 °C for 8 h. After the crosslink, chloroform was used to wash out the PHBV at 70 °C for getting ultra-porous UPM/PHBV fibers. In order to compare the weight loss behavior, the pure UPM and PHBV fibres were also prepared with the same method.

Loading Efficiency

To determine the drug loading efficiency, One gram chloroform-etched UPM/PHBV nanofibres were dipped into 50 mL TH/PBS (*p*H 7.4) solution with TH concentration of 0.1 g/mL. The solution was kept at constant temperature of 37 °C. The loading efficiency (%) was described by the following equations:

$$\text{Loading efficiency (\%)} = (M_1/M_0) \times 100 \quad \ldots(1)$$

where M_0 is the mass of pure material for carrying drug; M_1 , the mass of the drug loaded.

Characterization

The morphology of fibres was observed using a field emission scanning electron microscope (FE-SEM, JSM-6335F, JEOL) after platinum coating with an ion sputter.

Results and Discussion

UPM/PHBV Nanofibres Composite

It is observed that fibre cannot be fabricated from high UPM/PHBV weight ratio (10:1) using electrospinning technique. As the UPM/PHBV ratio decreases to 4: 1, the ultra-fine nanofibres are obtained. Figure 1 shows FE-SEM images of electrospun UPM/PHBV fibres with various UPM/PHBV weight ratios (4:1, 2:1 and 1:1). The fibres diameters increase from 700 nm to 1400 nm with the increase of UPM/PHBV ratio for preparing the nanofibres composite. It is remarked that the surface of as-spun UPM/PHBV fibres is ultra-smooth without any hole.

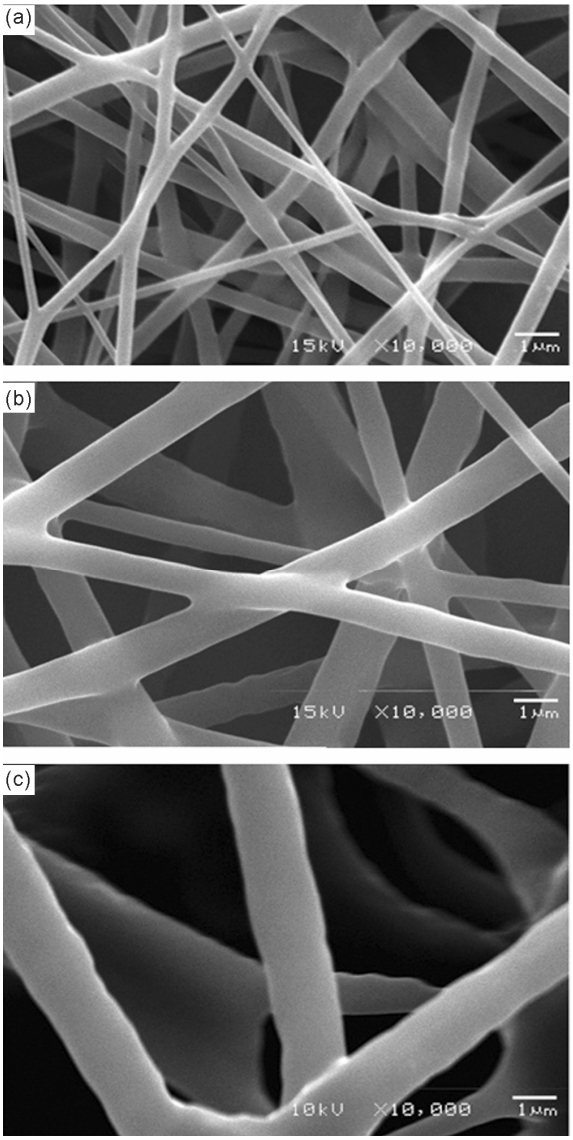

Fig. 1—FE-SEM images of nanofibres composite with various UPM/PHBV ratios (a) 4:1, (b) 2:1, and (c) 1:1. The solid contents in electrospun solutions were fixed to 10.0 wt%

Table 1—Porosity and specific surface area of electrospun UPM/PHBV nanofibrous membrane

Sample	PHBV mass fraction, %	Porosity %	Specific surface area, m^2/g
1	2	55.67	20.42
2	3.3	42.81	15.70
3	5	32.65	12.88

Porosity and Specific Surface of Nanofibrous Mats

The porosity and specific surface of the electrospun UPM/PHBV nanofibrous mats have been measured by an automatic mercury porosimeter, and the results are listed in Table 1. Both the porosity and the specific surface decrease with the increase in PHBV content in the nanofibrous mats. Sample 1 shows the largest porosity(55.67 %) as this sample has the smallest diameter of 200 nm. The porosity of the nanofibrous mats is related with the interfibrillar voids. Nanofibres with smaller diameter lead to larger amounts of voids when they interconnect to form mats and thus show larger porosity. Sample 2, which is fabricated from the spinning solution with the UPM/PHBV = 2:1 (w/w), shows a porosity of 42.81 %, lower than that of sample 1, due to its larger diameter. Sample 3 has even smaller porosity (36.25 %) as its diameter is reached to 1400 nm. The specific surface of the electrospun UPM/PHBV nanofibrous mats exhibites similar behavior, i.e., it decreases with the increase of fibre diameter in a more evident way, which is also ascribed to the reduced porosity caused by increasing fibre diameter. The specific surface of the electrospun UPM/PHBV nanofibrous mats can be as large as $20m^2/g$, confirming the large specific surface characteristic of electrospun nanofibrous mats.

Solvent Etching

UPM and PHBV pure fibres have been etched using chloroform for various time periods. As shown in Fig. 2, PHBV fibres after heat-treatment could easily dissolve in chloroform; but the thermal crosslinked UPM fibres can hardly be destroyed and maintained ~95 % after 20 h etching by chloroform. It is also demonstrated that the temperature significantly affects the etching process. Most of PHBV is dissolved at 70 °C within 8 h, while it took much longer time of 20 h at 30 °C.

Figure 3 shows the FE-SEM images of porous fibres obtained after partly washing out of PHBV from UPM/PHBV nanofibres composite by chloroform. Prior to washing process, UPM/PHBV nanofibres are heat-crosslinked at 90 °C for 8 h. FE-SEM images indicate that the porosity of UPM

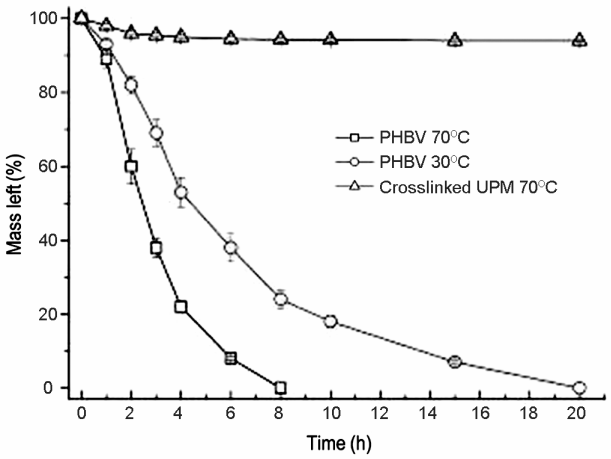

Fig. 2—PHBV and UPM mass loss in solvent

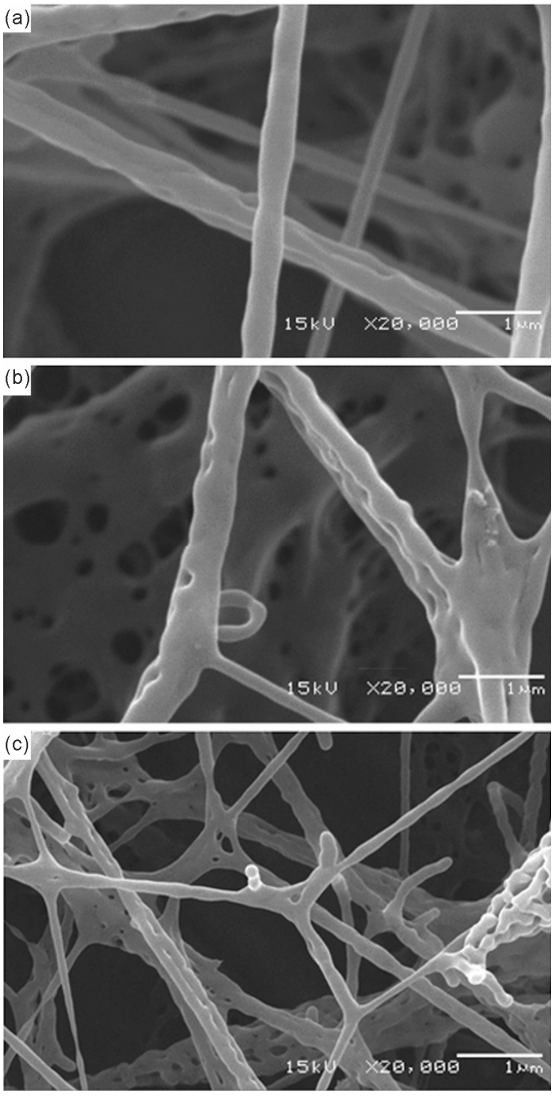

Fig. 3—FE-SEM images of UPM/PHBV fibres after etching using chloroform for 1 h at 70°C

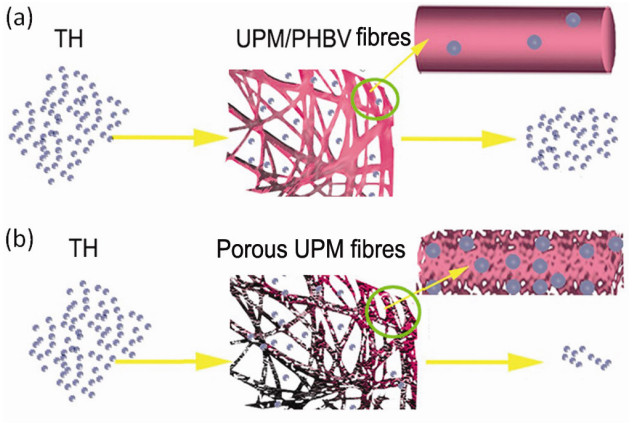

Fig. 4—Tetracycline Hydrochloride (TH) absorption in electrospun fibre [(a) Etching UPM/PHBV fibres (b) Pure UPM fibres]

fibres increases with the increase in PHBV ratios in their nanofibres composite. Therefore, it is reasonable to believe that the porous structure is formed by dissolving PHBV in chloroform and the UPM and PHBV molecules are separated in the electrospinning process but failed to blend uniformly.

In Vitro Drug-loading Efficiency

The porous structure theoretically increases the specific surface area of electrospun nanofibres; and the tiny holes on nanofibres help to capture small molecules such as drugs or proteins, as schematically shown in Fig. 4. As shown in Table 2, the drug loading efficiency of porous fibres increases from 1.1 % to 4.2 % with increasing the weight ratios of PHBV in the composite nanofibres. On the contrast, the TH loading efficiency of pure UPM fibres after heat-crosslinking is found to be only 0.6 %. Therefore, the solvent etching technique has great potential to be used in developing novel drug delivery system or water filter.

In this study, ultra-porous fibres have been produced by partly washing out PHBV from the thermal crosslinked electrospun UPM/PHBV fibrous composite using chloroform. FE-SEM images show that the composite fibres after etching have lost the original smooth surface but show much more porous morphology. TH is used as the module drug to test the drug-loading efficiency. The results demonstrate that the etching UPM/PHBV fibres have better drug-loading efficiency than pure UPM fibres.

Table 2—Drug absorption efficiency of UPM nanofibrous mats

Nanofibre samples UPM/ PHBV	Treatment	Loading efficiency %
1:1	Washed by chloroform	4.2
2:1	Washed by chloroform	3.3
4:1	Washed by chloroform	1.1
1:0	Without washing	0.6

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