

Chitosan Nanoparticles Self-Assembled from Electrospun Composite Nanofibers

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Abstract

Molecular self-assembly has been intensively investigated for “bottom-up” nanofabrication in recent years. A strategy that offers simple routes to functional nano-scale objects directly from templates through molecular self-assembly may lead to the development of new advanced materials for nanotechnology. Electrospun nanofibers can be good templates for manipulating molecular self-assembly by virtue of their nanometer confinement effect and the formulation of their components into a composite material. One-dimensional nanofiber composites of hydrophilic polyvinylpyrrolidone (PVP) and chitosan (CS) were successfully prepared through an elevated temperature electrospinning process. Scanning electron and transmission electron microscopy observations indicated that the fibers have an average diameter of 77 ± 11 nm with a homogeneous inner structure. Differential scanning calorimetry and X-ray diffraction results demonstrated that PVP and CS were in an amorphous state in the nanofibers, indicating they were mixed on the molecular scale. IR spectra revealed that second-order hydrogen bonding and electrostatic interactions played a fundamental role in promoting the structural homogeneity of the amorphous nanofiber composites. CS nanoparticles of about 10 nm in diameter are spontaneously self-assembled *in situ* when the nanofibers are added to water. Through a combination of “top-down” electrospinning and a “bottom-up” molecular self-assembly, a brand-new process has been developed for preparing polymer nanoparticles *in situ*.

Keywords: Polymer composites; Molecular self-assembly; Nanoparticles; Nanofibers; Electrospinning; Chitosan

Introduction

Molecular self-assembly has been exploited intensively for the design and fabrication of nanostructures, leading to the formation of advanced materials in a “bottom-up” manner [1,2]. However, sophisticated methodologies are often required to assemble and organize the molecules into nano scale objects. This has the inevitable result that mixture of different products form, owing to a lack of control on the molecular scale. New methodologies and mechanistic insights for precisely controlling molecular assemblies are important topics of research in this interdisciplinary field of science [3,4]. Nature solves this problem by using templates to control both molecular synthesis and accurate supramolecular self-assembly [5]. A strategy that offers simple routes to functional nano-scale objects directly from templates through molecular self-assembly may lead to the development of new advanced materials for nanotechnology.

Self-noncovalent or weakly covalent interactions are crucial in controlling the molecular self-assembly process. Important forces for self-assembly include van der Waals and Casimir forces, electrostatic forces, π - π and hydrophobic interactions, hydrogen and coordination bonds, convective, shear, magnetic, electrical and optical, colloidal and capillary forces [6]. Ensuring that the building molecules assemble themselves correctly, however, is not an easy task. There are mainly two reasons for this: (1) the forces involved are very small, and hence the self-assembling molecules can easily get trapped in undesirable conformations [7]; (2) self-assembly requires the components to be mobile, and often the building block molecules in the fluid carrier medium move randomly under Brownian motion. Thus, there is little precise control over the transport and contact of the building blocks on the molecular scale. In attempts to achieve control, the normal route available is to agitate the solution of building blocks with changes in temperature and viscosity [8,9].

Polymer composites have attracted considerable attention because of their ability to produce high-performance materials with enhanced or novel properties [10]. As a simple one-step top-down process for preparing one-dimensional (1D) polymer nanofibers, electrospinning is a powerful technique. It allows the facile preparation of nano scale polymer composites owing to rapid drying of the carrier solution, and favorable interactions of the functional components with the filament-forming polymer matrix [11-13]. It has been demonstrated that electrospun nanofiber composites are good templates for directly manipulating the self-assembly of small molecules into solid lipid nanoparticles and empty liposomes [14,15]. The nanofibers are thought to promote this process owing to their unique properties, including their continuous 3D web structure, thin diameter, large surface area, and high porosity [16-19].

Chitosan (CS) is a natural polymer with excellent biocompatibility, high biodegradability, good ecological safety, and low toxicity. It has versatile biological functions including antimicrobial activity, and low immunogenicity. CS has therefore become of great interest as a new functional biomaterial with significant potential in numerous fields [20]. In particular, CS nanoparticles have gained worldwide attention as drug delivery systems because of their high stability, low toxicity,

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and the possibility of versatile routes of administration. Several methods have been reported in the literature for the preparation of CS nanoparticles [21,22].

In the present study, the hydrophilic polymer polyvinylpyrrolidone (PVP) has been used as a filament-forming matrix upon which to mount CS building blocks, forming a polymer composite. PVP-CS nanofibers were prepared using an elevated temperature electrospinning process. The electrospun fibers were subsequently used as templates to manipulate the molecular self-assembly of CS nanoparticles.

Experimental

Materials

Polyvinylpyrrolidone K60 (PVP, $\overline{M}_w = 360,000$) was purchased from Shanghai Yunhong Pharmaceutical Aids and Technology Co., Ltd., Shanghai, China. Chitosan (CS, degree of deacetylation 91%) was provided by the Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Analytical grade formic acid and methanol were purchased from the Shanghai Shiyi Chemicals Reagent Co., Ltd. (Shanghai, China). Water was doubly distilled before use.

Electrospinning

One gram of CS was dissolved in 40 ml of formic acid. This solution was then diluted by adding 60 ml methanol, and 9 g PVP K60 was added to the solutions to prepare the co-dissolving spinning liquid.

A high voltage power supply (Shanghai Sute Electrical Co., Ltd.) allows the provision of spinning voltages in the range 0~60 kV. The diameter of the metal syringe needle used for electrospinning was 0.5 mm. The earthed electrode was connected to a metal collector wrapped with aluminum foil.

Elevated temperature electrospinning processes were carried out according to our previous work [23,24]. An electric heating film was wrapped around the glass syringe containing the spinning solution. The syringe and solution were then directly heated to a pre-determined temperature. The electric heating film was enveloped with asbestos to ensure heat insulation.

Optimum spinning conditions were found to be as follows. A fixed electrical potential of 18 kV was applied across a distance of 15 cm between the syringe tip and the collector. The feed rate was controlled at 0.2 ml h⁻¹ by a single syringe pump (Cole-Parmer, USA). Electrospinning was carried out at 50 ± 2 °C. The resulting composite nanofiber mats were collected and placed in a desiccator.

Characterization of polymer nanocomposites

The morphologies of the nanofibers were assessed using a S-4800 field emission scanning electron microscope (FESEM; Hitachi, Tokyo, Japan). The average fiber diameter was determined from FESEM images by measuring the diameters of the nanofibers at more than 100 different points, using the Image J software (National Institutes of Health, Bethesda, USA). Prior to FESEM, samples were carbon sputter-coated under argon for 40 s.

A JEM 2100F field-emission transmission electron microscope (TEM; JEOL, Tokyo, Japan) was used to study the nanofibers' inner texture. TEM samples were prepared by fixing a lacey carbon coated copper grid on the metal collector. Nanofibers were spun directly onto the grid.

Differential scanning calorimetry (DSC) analyses were carried

out using an MDSC 2910 differential scanning calorimeter (TA Instruments, New Castle, USA). Sealed samples were heated at 10°C min⁻¹ from 20 to 250°C under a flow of nitrogen gas (40 ml min⁻¹). X-ray diffraction patterns (XRD) were obtained on a D/Max-BR diffractometer (Rigaku, Tokyo, Japan) with Cu K α radiation over the 2 θ range 5-60° at 40 mV and 30 mA.

Attenuated total reflectance Fourier transform infrared (ATR-FTIR) analysis was performed on a Nicolet-Nexus 670 FTIR spectrometer (Nicolet Instrument Corporation, Madison, USA) over the range 500-4000 cm⁻¹ and at a resolution of 2 cm⁻¹.

Self-assembly of CS nanoparticles

A drop of water from a micro-injector was placed on a sample of electrospun fibers collected on a copper grid with a carbon supporting film, and naturally dried. TEM images of the self-assembled CS nanoparticles were recorded on the JEM 2100F TEM instrument.

Results and Discussion

Preparation of the electrospun nanofibers

The electrospinning of CS is a challenging task. There is high variability in material sources, and CS has inherently high inter- and intra-chain hydrogen bonding. These factors, coupled with its high solution viscosity at low concentrations and limited solubility in organic solvents, make the spinning process non-facile [25-27]. Nevertheless, some research groups have succeeded in the preparation of CS based composite fibers by blending it with polymers that have good electrospinnability such as polyethylene oxide (PEO) [28], polyvinyl alcohol [29], collagen [11] and polyamide-6 [30].

Raising the temperature of the solutions used for electrospinning has been found to have little influence on the effective chain entanglements in the working solution [31]. Control of these entanglements is a prerequisite condition for the preparation of uniform fibers, in order to prevent capillary breakup and to subdue Rayleigh instability. However, raising the temperature should decrease solution viscosities and surface tensions, and simultaneously increase conductivities. All these factors will help to improve electrospinnability, and to facilitate preparation of high quality composite nanofibers [24]. The Kit group has successfully prepared CS-PEO composite nanofibers with diameter of 80 ± 35 nm and CS-polyacrylamide composite nanofibers with diameter of 307 ± 67 nm using an air-assisted heating unit to heat the polymer solutions [32].

PVP has good electrospinnability in several solvents, including water, ethanol, methanol and chloroform [25]. Because of the numerous -C=O groups in the PVP molecules, it can form complexes with a wide variety of materials that can provide protons; this allows the two species to interact through hydrogen bonds. Blended films of CS and PVP have been reported in the literature [33,34]. Based on this body of knowledge, PVP-CS composite electrospun nanofibers prepared using an elevated temperature electrospinning were investigated. The co-dissolving solution of CS and PVP in formic acid and methanol was clear with a light yellow color.

Characterization of the PVP-CS nanocomposites

FESEM images of the composite nanofiber mat surface are shown in Figure 1a. It is clear that the fibers have uniform structures without any "bead-on-a-string" morphology. They have smooth surfaces, with no particles separating out from the nanofiber matrix. Statistical results from the Image J software indicated that the fibers have an average

diameter of 77 ± 11 nm. TEM images of the nanofibers (Figure 1b) suggested that they had a homogeneous inner structure, reflected by the uniform gray color of both the upper and lower nanofibers. These data suggest that CS molecules are evenly distributed throughout the PVP matrix.

DSC and XRD analyses were carried out to investigate the physical status of the PVP and chitosan components in the nanofibers. DSC thermograms of PVP, CS and the composite nanofibers are shown in figure 2. PVP displayed a broad endotherm owing to dehydration; this lies between 80°C and 120°C , with a peak at 86°C . PVP is a polymer, and can exist in a glassy or a rubber-like state. The change from one state to the other is visible in the DSC as a small glass transition from 170 to 180°C [24].

For pure CS, the peak observed in the DSC thermogram at around 81.2°C is attributed to the water-induced β relaxation, while the transition peak appearing at 160.3°C should correspond to the α -crystal structure relaxation [35]. The DSC data for the composite nanofibers show that both the CS peak at 160.3°C and the PVP transition from 170 to 180°C have disappeared, suggesting an amorphous composite was formed.

XRD patterns of PVP, CS and the composite nanofibers are given in figure 3. The PVP diffraction pattern exhibits a diffuse background pattern with two diffraction halos, which demonstrates that the polymer is amorphous. CS has two crystalline forms (α and β), both of which crystallize with monoclinic symmetry. The two diffraction peaks seen at $2\theta = 11.0^\circ$ and 20.0° correspond to the α polymorph of chitosan [36].

However, the diffraction pattern of the fibers contains neither of the signature diffraction peaks of CS, suggesting no crystalline CS was present in the nanofibers. Both the DSC thermograms and XRD patterns concurred with the TEM observations, demonstrating that

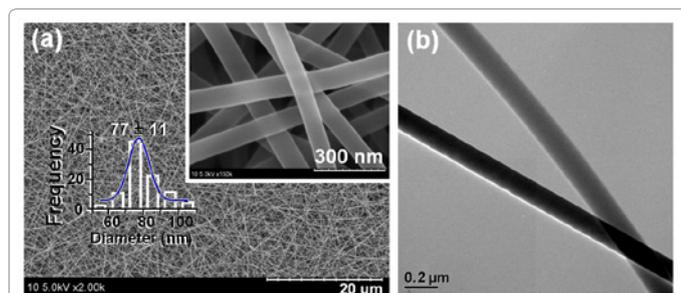


Figure 1: Morphologies of the electrospun nanofibers: (a) FESEM images; (b) TEM images.

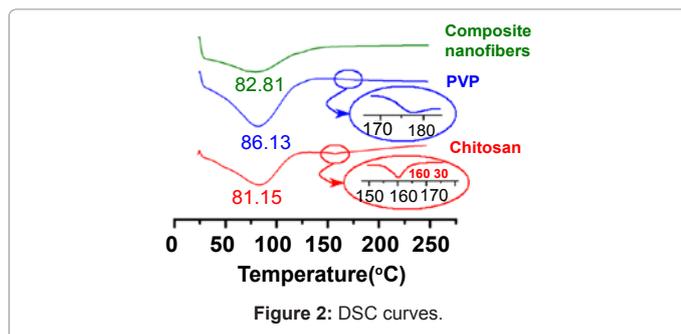


Figure 2: DSC curves.

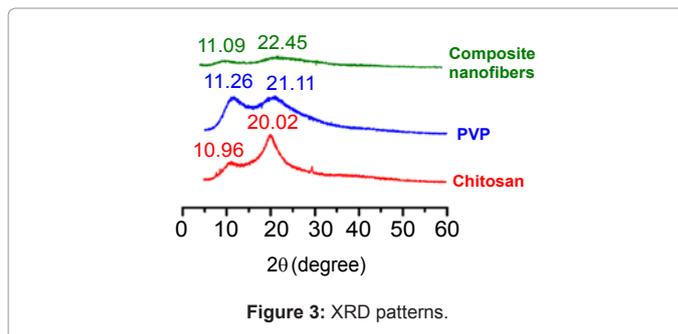


Figure 3: XRD patterns.

PVP and CS were in an amorphous state in the nanofibers. These results all indicate that the components were mixed on the molecular scale, and the formation of crystalline CS was avoided.

To elucidate the interactions between PVP and CS in the nanofibers, ATR-FTIR analyses were carried out. ATR-FTIR spectra of pure PVP, CS and their electrospun composite are included in figure 4. The presence of hydrogen bonding interactions between PVP and CS in the composite nanofibers can be inferred from the shift to lower wavenumbers of peaks assigned to the C=O stretching vibrations of PVP (from 1666 cm^{-1} in pure PVP to 1659 cm^{-1} in the fiber), and the disappearance of the CS peaks at 1070 cm^{-1} (corresponding to C-O-C bends) [11]. The -OH groups and $-\text{NH}_2$ groups in CS are capable of forming hydrogen bonds with the $-\text{C}=\text{O}$ groups in PVP.

In addition to hydrogen bonding, PVP and CS may also interact with each other through electrostatic interactions between the negatively charged PVP oxygen atom ($\text{N}^+ = \text{C}-\text{O}-$) and the ionizable amino group of chitosan [37].

Second-order hydrogen bonding and electrostatic interactions are considered to have played a fundamental role in promoting the structural homogeneity of the amorphous nanofiber composites. The time taken to generate the fibers by electrospinning was only several tens of milliseconds [24]. The rapid evaporation of the solvent and the favorable interactions between PVP and CS resulted in the formation of a solid solution in the form of a three-dimensional continuous web of nanofibers. In the fibers, CS molecules are arranged in linear conformations; this results from the templating role of the PVP molecules and the electrical drawing force during the electrospinning process. No phase separation occurred, and no CS crystalline lattice formed. It can therefore be concluded that electrospinning is a useful method for preparing highly homogeneous polymer nanocomposites.

Self-assembled CS nanoparticles

TEM images of self-assembled CS nanoparticles formed by adding a drop of water to the PVP-CS nanofibers are given in Figure 5. During the drying process, the water soluble PVP formed a transparent membrane, leaving the water insoluble CS to self-aggregate into nanoparticles based on the principle of "like prefers like" [7]. The CS nanoparticles thereby formed have a diameter range of 10 ± 2 nm. This is around 10% of the nanofiber diameter, and corresponds closely to the content of CS in the polymer composite.

Self-assembly relies primarily on diffusive transport in solution [8,9] Prepositioning the building blocks homogeneously on a polymer matrix to form a nanocomposite can improve our capability to precisely manipulate molecular transport and contact on a confined micro-scale region. Thus, self-assembly based on 1D nanocomposites

should be easier and more controllable than traditional methods in which agitations at the macro scale are exploited in attempts to control molecular diffusion and to bring the components into contact [8].

The “dissolution” process of the composite fibers in water is essentially a self-assembly process. The 1D fiber acted as templates, and synergistic influences of various favorable interactions during dissolution promoted the formation of CS nanoparticles. Such interactions will include: hydrophobic repulsion from water, inter- and intra-chain hydrogen bonds of the CS molecules, and electrostatic interactions.

As illustrated in figure 6, the self-assembly processes can be summarized as follows: (1) After the 1D nanofibers come into contact with water, strong interactions resulting from hydrogen bonding between the C=O group of PVP and water molecules causes the water to liberate the CS molecules from the PVP chains. Concomitantly, the CS molecules change their conformations from linear to folded owing mainly to inherently high inter-chain hydrogen bonding. (2) The PVP fiber matrix further absorbs water, swells, and is gradually disentangled. The folded CS molecules are concentrated within the framework of the swelling nanofibers owing to hydrophobic repulsion from water. (3) Finally, the folded CS molecules co-aggregate into nanoparticles (as a result mainly of the strong intra-chain hydrogen bonding interactions), and are freed into the dissolution medium when the fiber templates completely collapse and the PVP molecules disentangle and dissolve.

The whole assembly process takes place spontaneously owing to the highly hygroscopic and hydrophilic properties of PVP, the small diameter of the 1D nanofibers, and the 3D continuous web structure of the nanofiber mats. These properties facilitate the penetration of water molecules into the fibers, and the diffusion of PVP molecules into the bulk dissolution medium.

Considerable research efforts have been directed towards developing safe and efficient CS-based particulate drug delivery systems (DDS). This study demonstrates an innovative new process for the preparation

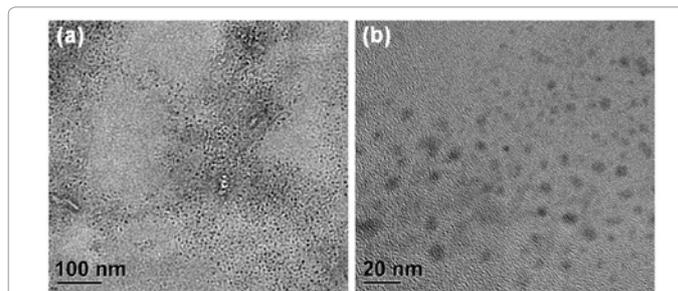
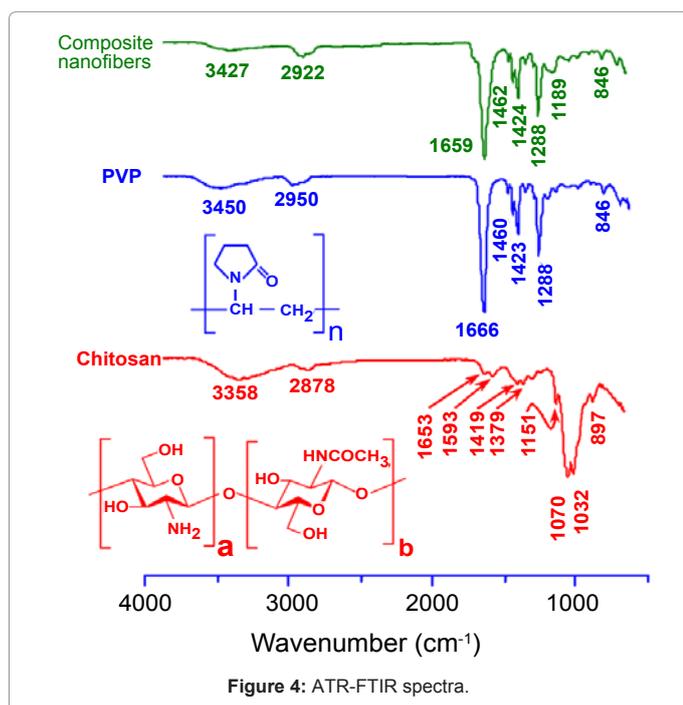
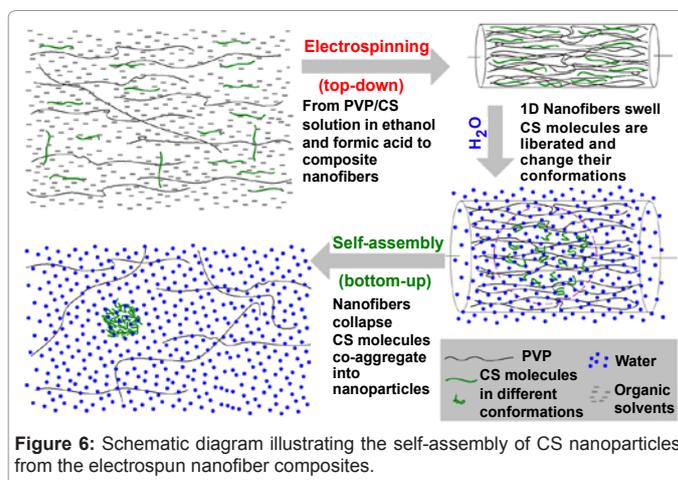


Figure 5: TEM images of the self-assembled CS nanoparticles with different magnifications: (a) 50,000 \times ; (b) 200,000 \times .



of CS nanoparticles. Electrospun nanofibers are facile to prepare, and their properties can very easily be tailored in terms of secondary microstructure, components, and composition. Thus, pharmaceutical ingredients such as drugs, diagnostic agents and functional peptides and proteins could easily be incorporated into the nanofibers with CS for the development of novel CS-based DDS. Cross-linking agents could also be loaded into the polymer composite to regulate drug release from the self-assembled CS-based drug nanoparticles.

Conclusions

Polymer nanocomposites of PVP and CS were successfully prepared using an elevated temperature electrospinning process. The one-dimensional electrospun nanofibers produced proved to be excellent templates for manipulating the self-assembly of CS molecules. CS nanoparticles are spontaneously self-aggregated upon the dissolution of the PVP matrix in water. The homogeneous pre-positioning of the macromolecular entities in a polymer matrix therefore offers a facile method for controlling self-aggregation into nanoparticles, following removal of the matrix polymer.

Over the past decades, there has been considerable interest in exploiting lipid- or polymer-based nanoparticulate DDS for improving the pharmacological and therapeutic properties of drugs administered parenterally [21,38]. The present study demonstrates not only a new method for synthesizing polymer nanoparticles, but also opens a new process to prepare man-made self-assembly materials and polymer-based nanoscale DDS. This simple and efficient synthetic route to polymer nanoparticles may lead to a wide variety of new functional materials for nanotechnological applications.

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