Electrospun UV-responsive supramolecular nanofibers
from a cyclodextrin–azobenzene inclusion complex†

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A combination of the unique hosting properties of cyclodextrins (CDs) and the peculiar UV-responsive *trans*–*cis* isomerization of the guest molecule azobenzene has endowed light-responsibility of the inclusion complex (IC). The IC of 4-aminoazobenzene (AAB) and hydroxypropyl- β -cyclodextrin (HP β CD), with its inherent viscosity from hydrogen bondings between CDs and π – π stacking between AABs, was electrospun into nanofibers from water without using any carrier polymer matrix. The integrity of electrospun ICs was proven by thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), together with Fourier transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD). The homogeneous distribution of HP β CD–AAB–IC was confirmed by surface chemistry mapping using time-of-flight secondary ion mass spectrometry (ToF-SIMS). The UV response of ICs prior to, during and post electrospinning was investigated. UV irradiation prior to electrospinning caused precipitation of AAB from the aqueous IC solution. UV irradiation during electrospinning flight demonstrated the interruption of ICs and consequently broader diameter distributions were obtained. Post-spinning UV irradiation induced topography and adhesion force changes on the electrospun nanofiber surfaces, demonstrated by *in situ* atomic force microspectroscopy (AFM) quantitative nanomechanical mapping. The present study is the first case where the supramolecule with stimuli response was electrospun into nanofibers with retained activity.

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Introduction

Cyclodextrins (CDs) have been extensively studied for over half a century¹ mainly because of their peculiar hosting properties. The truncated cone structure made of glucopyranose units has endowed CDs a unique combination of a hydrophilic outer surface, where the hydroxyl groups are located, and a hydrophobic inner cavity to host various hydrophobic molecules and form water-soluble inclusion complexes (ICs). These biocompatible, cyclic oligosaccharides do not elicit immune responses and have low toxicities in animals and humans. Therefore, CDs are used extensively to host various drugs in pharmaceutical applications for numerous purposes, including the improvement of bioavailability, efficacy, specificity, tolerability and therapeutic index of corresponding drugs.²

Upon oral and parenteral administration, drugs appear to be rapidly dissociated from CD ICs, where diffusion upon dilution

appears to be the major release mechanism.³ While drugs ideally are released in a controlled manner from a formulation, the concept of controlling the release upon external stimulus is extremely desirable.⁴ A particularly intriguing possibility is offered by light-responsive materials allowing remote and accurate operation that can easily be focused into specific areas of applications. The photo-response of these materials is based on the photo-isomerization of constituent molecules that undergo a large conformational change between two states in response to the absorption of light at two different wavelengths.⁵ Typically, the *trans*–*cis* isomerization of azobenzene chromophores,⁶ which reversibly interconvert between an extended, thermally relaxed *trans* isomer and a higher energy *cis* or “bent” isomer, gives rise to changes in the dipole moments, polarity, or shape of the molecules. Thus, these azobenzene chromophores have opened up a large variety of utilizations in the synthesis of new intelligent nanomaterials.⁷ The geometry change associated with azobenzene photoisomerization (~ 0.7 nm) has been used to control protein activity by light by attaching azobenzene to ligands.^{7a} Azobenzenes have also been applied to ion channels in the nervous system to facilitate optical control of electrical activity in neurons.⁸

Light-responsive azobenzene has been found to be able to form inclusion complexes (ICs) with CDs in its *trans* state,⁹ while its *cis* form is too bulky. Such a supramolecular

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Scheme 1 Electrosincking of UV responsive HPβCD-AAB-ICs.

system has thus been further explored because of its light responsibility.¹⁰

Electrospinning is a polymer processing technique that produces continuous nano- to microscale fibers through the action of an external electric field imposed on a rich variety of polymer melts or solutions that include synthetic or natural polymers, or composite polymer blends with small molecules. It is crucial to the presence of polymer chain entanglements in the charged fluid that ensures the fluid does not break up into droplets but forms a stable jet when the electrostatic repulsive forces on the fluid surface overcome the surface tension.¹¹ Nevertheless, supramolecular chemistry further pushes the technique beyond the limited choice of materials within polymers; instead small amphiphiles such as phospholipids¹² and gemini surfactants,¹³ self-assembled diphenylalanine,¹⁴ and supramolecular polymers from heteroditopic monomers¹⁵ have been successfully electrospun into fibers, since these molecules can form supramolecules and entangle in a fashion similar to polymers.

Unlike classical amphiphiles, CDs show a low polar character, indicated by their cohesion energy distribution, and have no dipolar or vectorial contribution but a quadrupolar character.¹⁶ The self-assembly of CDs had thus not been taken into account until the last decade, where some evidence of self-aggregation of CDs in solution was observed by different microscopies, especially at concentrated solutions.¹⁷ It is thus intriguingly interesting that recently the electrospinning of CDs¹⁸ and CD-ICs¹⁹ has been accomplished without any polymer matrix. Furthermore, there is still very few known concerning the photo-response behavior of electrospun nanofibers based on CDs.²⁰

Here we describe the first study of electrospun UV-responsive supramolecular nanofibers from ICs of hydroxypropyl-β-cyclodextrin (HPβCD) with 4-aminoazobenzene (AAB) (Scheme 1). ToF-SIMS was utilized for surface chemical mapping. Thermo-physical properties of the electrospun ICs were studied by TGA and DSC, while the structural analyses were performed by FTIR and XRD. The UV response of ICs prior to, during and post electrospinning was investigated, applying AFM quantitative nanomechanical mapping.

Results and discussions

Electrospinning of HPβCD-AAB-ICs

Clear orange HPβCD-AAB-IC solutions were successfully prepared and electrospun without the addition of any carrier

polymeric matrix. CD-AAB ICs are known to be able to aggregate through hydrogen bondings between CDs and π-π stacking between AABs.⁹ The representative SEM images of the electrospun HPβCD-AAB-IC nanofibers are displayed in Fig. 1. Beads of HPβCD-AAB-IC (Mat I, 1 : 0.3 molar ratio, HPβCD 100 w/v%) (Fig. 1a) were obtained with diameters in the range of 0.8–5 μm due to the low entanglement of the assembled molecules. In the case of HPβCD-AAB-IC (Mat II, 1 : 0.9 molar ratio, HPβCD 120 w/v%), the beads were stretched and connected by nanofibers with the fiber diameter range of 200–900 nm (Fig. 1b). HPβCD-AAB-IC (Mat III, 1 : 0.7 molar ratio, HPβCD 140 w/v%) resulted in nano-microfibers of diameters of 0.2–1.7 μm with very few elongated beads (Fig. 1c). At higher concentrations, bead-free electrospun fibers (Fig. 1d) having the fiber diameter range of 0.6–1.5 μm with an average fiber diameter of $1.08 \pm 0.29 \mu\text{m}$ were obtained with HPβCD-AAB-IC (Mat IV, 1 : 1 molar ratio, HPβCD 130 w/v%). Table 1 summarizes the morphology information together with their diameter distributions.

Fig. 1 SEM images of electrospun HPβCD-AAB-ICs.

Table 1 Electrospinning of HPβCD-AAB-ICs

Mat	% HPβCD (w/v)	% AAB (w/v)	HPβCD-AAB molar ratio	Morphology	Bead/fiber diameter (nm)
I	100	4	1 : 0.3	Beads	$2.32 \pm 1.14 \mu\text{m}/$ —
II	120	12	1 : 0.9	Beaded nanofibers	$1.93 \pm 1.24 \mu\text{m}/$ $0.46 \pm 0.17 \mu\text{m}$
III	140	12	1 : 0.7	Nano-microfibers (with very few elongated beads)	—/ $0.94 \pm 0.23 \mu\text{m}$
IV	130	16	1 : 1	Nano-microfibers	—/ $1.08 \pm 0.29 \mu\text{m}$

ToF-SIMS spectra and chemical mapping

ToF-SIMS was applied to identify the molecules and map their distribution on the surfaces of individual beads or fibers with a depth resolution of 1–2 nm. The principal component analysis (PCA) clearly shows the intensive signals from HPβCD, such as m/z 31 (CH_3O^+), m/z 43 ($\text{C}_2\text{H}_3\text{O}^+$), m/z 57 ($\text{C}_3\text{H}_5\text{O}^+$), m/z 85 ($\text{C}_4\text{H}_5\text{O}_2^+$), m/z 127 ($\text{C}_6\text{H}_7\text{O}_3^+$), m/z 143 ($\text{C}_7\text{H}_{11}\text{O}_3^+$), m/z 203 ($\text{C}_{10}\text{H}_{19}\text{O}_4^+$) and m/z 221 ($\text{C}_9\text{H}_{17}\text{O}_6^+$, monomer), and signals from AAB, such as m/z 59 ($\text{C}_3\text{H}_9\text{N}^+$), m/z 77 (C_6H_5^+), m/z 92 ($\text{C}_6\text{H}_6\text{N}^+$), m/z 107 ($\text{C}_6\text{H}_7\text{N}_2^+$), and m/z 198 ($\text{C}_{12}\text{H}_{12}\text{N}_3^+$, monomer) (Fig. 2).

The identified fragment ions originating from either HPβCD or AAB (Fig. 2) appear at unique nominal m/z values (Table 2). They can thus be used to obtain chemical maps of the distribution of HPβCD and AAB on the fiber surfaces. Individual nanofibers in Mat I (HPβCD–AAB = 1 : 0.3, HPβCD 100 w/v%) and Mat IV (HPβCD–AAB = 1 : 1 molar ratio, HPβCD 130 w/v%) were imaged using the chemical contrasts observed (Fig. 3). The TOF-SIMS chemical mapping results show that the ICs were homogeneously distributed and randomly oriented without preferential allocation. The cavity-on-bead structure in Mat I is probably due to that the lower inner pressure compared to ambient spinning conditions has built up from the CD ICs system which has a lower water content in the CD cavities.

Integrity of electrospun HPβCD–AAB-ICs

The thermal characterizations of the HPβCD–AAB-IC nanofibers were carried out by TGA and DSC techniques. The pure AAB and HPβCD powders were also analyzed for comparison.

Fig. 2 Representative positive ion ToF-SIMS spectra recorded from Mat IV. Major peak assignments are shown in red.

Table 2 Peak assignments derived from the positive ion ToF-SIMS spectra in Fig. 2

HPβCD (m/z)	31	57	85	97
	CH_3O^+	$\text{C}_3\text{H}_5\text{O}^+$	$\text{C}_4\text{H}_5\text{O}_2^+$	$\text{C}_5\text{H}_5\text{O}_2^+$
AAB (m/z)	27	39	59	65
	C_2H_3^+	C_3H_3^+	$\text{C}_3\text{H}_9\text{N}^+$	C_5H_5^+
HPβCD (m/z)	127	143	203	221
	$\text{C}_6\text{H}_7\text{O}_3^+$	$\text{C}_7\text{H}_{11}\text{O}_3^+$	$\text{C}_{10}\text{H}_{19}\text{O}_4^+$	$\text{C}_9\text{H}_{17}\text{O}_6^+$
AAB (m/z)	77	92	107	198
	C_6H_6^+	$\text{C}_6\text{H}_6\text{N}^+$	$\text{C}_6\text{H}_7\text{N}_2^+$	$\text{C}_6\text{H}_7\text{N}_2^+$

Fig. 3 ToF-SIMS chemical images of the HPβCD–AAB-IC Mats I (upper panel, area: 50 μm × 50 μm) and Mat IV (lower panel, area 500 μm × 500 μm). Column (a): HPβCD fragment ion images; column (b): AAB fragment ion images; and column (c): overlay images of column (a) and column (b).

TGA thermograms of pure AAB, HPβCD nanofibers, and HPβCD–AAB-IC fibers are depicted in Fig. 4a. The degradation of AAB started at about 122 °C, while the onset temperature for the HPβCD–AAB-IC Mat III was observed at 148 °C. Thus, the thermal degradation temperature of AAB in ICs has shifted to a higher temperature when compared to that of pure AAB. From the TGA data, the AAB amount was calculated to be 6.07%, which corresponds to a 1 : 0.7 molar ratio complexation between HPβCD and AAB, while the main weight loss (84%) observed at 300 °C belongs to HPβCD.

DSC is a useful technique for determining whether the guest molecules are included inside the CD cavities,¹⁹ since a thermal transition such as the melting point (T_m) of guest molecules would be observed if there were any free uncomplexed guest molecules present in the CD–IC system. The HPβCD–AAB-IC Mat III were also characterized by the differential scanning calorimetry (DSC) technique C (Fig. 4b) in order to verify whether the AAB was included in the CD cavities or not. The DSC thermogram of pure AAB showing a melting point about 122 °C is also given for comparison. The DSC thermogram of HPβCD–AAB-IC fibers did not show any melting peak for free AAB, indicating complete inclusion complexation AAB with HPβCD. The absence of a thermal event such as T_m for the guest molecule AAB in HPβCD–AAB-IC fibers correlates with the TGA

Fig. 4 (a) TGA spectra of the electrospun HPβCD–AAB-IC Mat III and the components AAB and HPβCD, (b) DSC spectra of the electrospun HPβCD–AAB-IC Mat III and AAB.

data (Fig. 4a), where the thermal degradation temperature of AAB in ICs shifted to a higher temperature.

Furthermore, as shown in FTIR spectra (Fig. S1†), characteristic peaks of AAB shifted from 1597 to 1602 cm^{-1} and from 1504 to 1508 cm^{-1} after forming ICs with HP β CD. HP β CD–AAB–IC fibers show no diffraction pattern for AAB in the XRD data (Fig. S2†). All these data support the findings of a true inclusion complexation in electrospun HP β CD–AAB–IC fibers, demonstrating the integrity of the ICs upon electrospinning.

UV-response

PRIOR TO ELECTROSPINNING. UV irradiation triggers the photoisomerization of AAB from the *trans* form to its *cis* form, and consequently the dissociation of the HP β CD–AAB–ICs. UV irradiation prior to electrospinning caused precipitation of AAB from the aqueous IC solution (Fig. S3†). The suspension could be switched back to the clear solution upon heating, indicating the re-association of the ICs. The switchability evaluation of ICs is, however, not applicable to the process of UV-electrospinning or the electrospun IC nanofibers.

UV-ELECTROSPINNING. Electrospinning under UV irradiation was further carried out. Significant increases of diameters and diameter distributions were observed, compared with electrospinning without UV irradiation (Table 3 and Fig. S4†). Because the self-assembly forces of the ICs consist of both hydrogen bondings between CDs and π – π stacking between *trans* AABs, the photo-isomerization of AAB to the *cis* form, and the subsequent dissociation of ICs would cause disturbance to the self-assembled supramolecular structure and further interrupt the inherent molecular entanglement for the electrospinning process. Thus electrospinning became unstable and the resulting beads (Mat UV-I and Mat UV-II) or fibers (Mat UV-III) demonstrated broader diameter distributions. Meanwhile, as the increase of the viscosity of the solution would hinder molecular mobility for IC dissociation, the changes of diameter and diameter distribution decreased when HP β CD–AAB concentration increased (Table 3).

IN SITU AFM QUANTITATIVE NANOMECHANICAL MAPPING (POST ELECTROSPINNING). AFM based quantitative nanomechanical mapping (QNM) is a novel AFM derivative technique allowing for simultaneous recording of topographical and mechanical properties, thereby determining the nanoscale mechanical stiffness of the fibers and tip–sample interaction.²¹ The UV response of the electrospun IC nanofibers was further characterized by *in situ* imaging using this technique. The overview topography image of a single fiber from HP β CD–AAB–IC Mat IV is

depicted in Fig. 5A, where the inset square indicates the further zoom-in position where the QNM was performed to investigate the local nanoscale structure. As shown in Fig. 5B and E, before and after *in situ* UV exposure, respectively, no polymeric fibrillar structure²² was observed in the zoom-in topography images. Meanwhile, the obtained uneven surface in Mat IV (Fig. 5B), which resulted from full stretching of those beads with cavities in Mat I (Fig. 1a), became smoother upon UV exposure (Fig. 5E), as summarized with the horizontal line profiles in Fig. 5D.

Furthermore, the tip–sample interaction force maps before and after *in situ* UV exposure, as shown in Fig. 5C and F, respectively, were recorded simultaneously. Under ambient condition of 44% humidity, a water layer was captured on the sample surface. Hence, the capillary phenomenon between the AFM tip and the sample appears each time when the tip interacts with the sample surface, which is reflected in the recorded values of the adhesion forces between the tip and the sample during the force mapping.²³ According to the adhesion force distributions extracted from Fig. 5C and F, it is clear that after UV exposure the tip–sample interaction force decreased from 10.66 ± 0.63 nN to 5.91 ± 0.42 nN. As known, *trans* azobenzene transformed to *cis* azobenzene upon UV exposure, which will be too bulky to remain inside the CD cavities and consequently needs to be released. While the resulting molecular movement changed the fiber surface topography, the hydrophobic nature of the released AAB also induced a decrease in the surface hydrophilicity. It is known that the less hydrophilic the sample is, the less water it is able to hold, and consequently the less adhesion force between the sample and the tip would occur. Therefore, the significant change in the topography and

Fig. 5 AFM quantitative nanomechanical mapping of the HP β CD–AAB–IC Mat IV before and after UV irradiation. (A): The overview of the fiber; the inset square indicates the position where AFM nanomechanical maps are recorded; (B and E): the topography images before and after UV exposure; (D): the horizontal line profiles across (B and E); (C and F): the corresponding tip–sample adhesion maps of (B and E) respectively; (G): the tip–sample adhesion force distribution before (10.66 ± 0.63 nN) and after UV exposure (5.91 ± 0.42 nN).

Table 3 Electrospinning of HP β CD–AAB–ICs under UV irradiation

Mat ^a	HP β CD–AAB molar ratio	Fiber morphology	Diameter (μm) without UV	Diameter (μm) with UV	Change in mean diameter (%)
UV-I	1 : 0.15	Beads	1.81 ± 0.94	4.04 ± 1.78	120.44
UV-II	1 : 0.3	Beads	2.32 ± 1.14	3.99 ± 2.48	74.14
UV-III	1 : 0.7	Nano-microfibers	0.94 ± 0.23	1.47 ± 0.49	55.32

^a UV-I: 100 w/v% HP β CD, 2 w/v% AAB; UV-II: 100w/v% HP β CD, 4 w/v% AAB; UV-III: 140 w/v% HP β CD, 12 w/v% AAB.

adhesion force upon *in situ* UV exposure is solid proof of the UV response of the electrospun HP β CD–AAB–IC fiber.

Conclusions

The present study is the first case where supramolecules with stimuli response were electrospun into nanofibers with retained activity. The integrity of electrospun HP β CD–AAB–IC was proven by TGA, DSC, together with FTIR and XRD. The lower water content in the CD cavities builds up a lower inner pressure during electrospinning, which caused the cavity-on-bead structure at a low concentration of ICs. The homogeneous distribution of HP β CD–AAB–IC was confirmed by surface chemistry mapping using ToF–SIMS.

The *trans*–*cis* isomerization of azobenzene triggered by UV light caused a significant change in the AAB molecular geometry and subsequently the dissociation from the ICs. The UV response of the ICs prior to, during and post electrospinning was investigated. UV irradiation prior to electrospinning caused precipitation of AAB from the aqueous IC solution. UV irradiation during electrospinning flight demonstrated interruption of the ICs and consequently broader diameter distributions were obtained. Post-spinning UV irradiation induced topography and adhesion force changes on the electrospun nanofiber surfaces, revealed by *in situ* AFM quantitative nanomechanical mapping.

Although the existence of CDs and their use in the pharmaceutical industry have been documented for decades, it is only recently that their exploration in applications beyond the solubilization and stabilization of small molecules has occurred. We believe the combination of the photo-responsibility from azobenzenes and the broad pharmaceutical applications of CD in a fibrous manner may flourish their potential in controlled drug delivery, sensors, and optical storage. Further study based on our previous study^{7d} and CD prodrug in this direction is currently underway.

Furthermore, the present novel findings again proved the simplicity, robustness, and versatility of the electrospinning technique, extending its great potential in a broad range of research areas.

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