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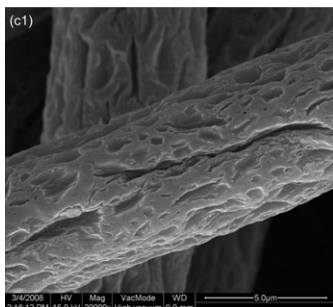
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Stimuli-responsive electrospun fibers and their applications

Chaobo Huang, Stefaan J. Soenen, Joanna Rejman, Bart Lucas, Kevin Braeckmans, Jo Demeester and Stefaan C. De Smedt*

In this critical review, an overview is given on recent advances in the development and application of stimuli-responsive electrospun nanofibers.

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CRITICAL REVIEW

Stimuli-responsive electrospun fibers and their applications

Chaobo Huang,^{†a} Stefaan J. Soenen,^{†ab} Joanna Rejman,^a Bart Lucas,^a
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Stimuli-responsive electrospun nanofibers are gaining considerable attention as highly versatile tools which offer great potential in the biomedical field. In this *critical review*, an overview is given on recent advances made in the development and application of stimuli-responsive fibers. The specific features of these electrospun fibers are highlighted and discussed in view of the properties required for the diverse applications. Furthermore, several novel biomedical applications are discussed and the respective advantages and shortcomings inherent to stimuli-responsive electrospun fibers are addressed (136 references).

1. Introduction

Electrospinning, also known as electrostatic spinning, is a straightforward, rather simple and highly versatile technique which allows generating (ultrathin) fibers from a variety of polymers and composite materials.^{1,2} The simplicity of the procedure, the possible large scale production and wide variety

in usable polymers, make electrospinning attractive for a wide range of biomedical applications such as tissue engineering, wound dressing, drug delivery and more.³ In polymer research, much progress is being made in the area of so-called stimuli-responsive polymers^{4–7} which can alter one or more properties such as *e.g.* morphology, strength or color upon exposure to external signals, such as pH, ionic strength or light.^{8–10} In the present work, the fusion of two highly interesting research topics, electrospinning and stimuli-responsive polymers, is addressed, presenting an up-to-date overview of the work done so far on stimuli-responsive electrospun fibers. Furthermore, some other emerging and attractive biomedical/pharmaceutical applications of electrospun fibers, such as encapsulation of living material like proteins or even whole mammalian cells and the use of electrospun fibers to protect

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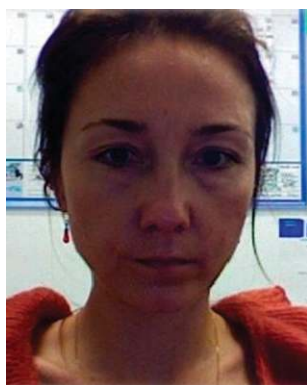
1 drugs against drug counterfeiting, are highlighted. In the final
conclusion section, the typical features of electrospun fibers
are discussed in view of their biomedical application.

5 1.1 History of electrospinning

Electrospinning in itself has been known for quite some
time.^{11,12} Back in 1745, Bose described the use of high electric
potentials to generate aerosols from fluid drops. In 1882, the
number of charges which are required to overcome the surface
tension of a droplet was calculated by Lord Rayleigh. The first
devices to spray liquids through the application of an electrical
charge were already patented by Cooley and Morton at the
beginning of the twentieth century. In a series of patents from
15 1934 to 1944, Anton Formhals was the first to describe
electrospinning of plastics.¹¹ In 1964, Taylor showed that
when the applied voltage exceeds a critical voltage, a stable

1 jet of liquid could be ejected from the suspended meniscus.
Later on, others applied this work on a wide variety of
polymeric systems in generating electrospun fibers.

Despite these early discoveries, electrospinning did not
become really popular until the late 1990's, possibly due to
the lower yield of fiber production compared with industrial
fiber spinning. From the late 1990's on, the booming of
nanotechnology led to the rediscovery of the potential use
of electrospinning for the production of nanometre-sized
diameter fibers from various polymers.⁹ Initialized by the
10 Reneker group, the popularity of electrospinning has
increased exponentially in the past 10 years as clearly reflected
from the number of publications (Fig. 1). This renewed
interest was further driven forward by the fact that people
began to realize that (a) electrospinning is a rather simple
15 method, (b) a wide variety in polymers and composites can be
used, (c) fibers have a high surface to volume ratio which may



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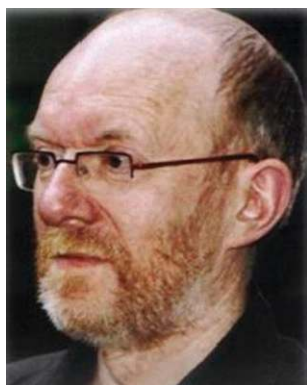
2007 she is employed by Ghent University, Faculty of
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to manipulate cellular characteristics.



Kevin Braeckmans

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Standards of the International
Pharmaceutical Federation
(F.I.P.) and since 1998 he is
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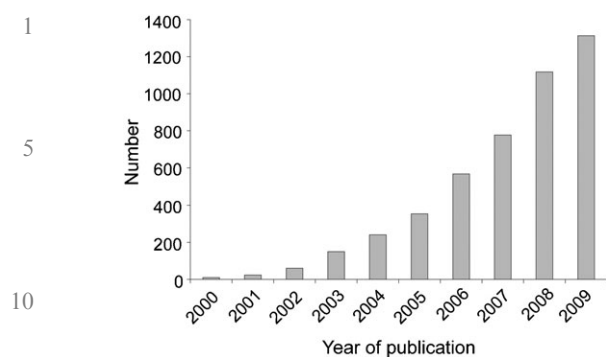


Fig. 1 Schematic representation of the annual number of publications on electrospinning over the last 10 years, following the ISI Web of Knowledge.

be beneficial for drug delivery or tissue engineering, (d) both random fiber webs as well as highly aligned fiber meshes can be designed, (e) a wide range of hydrophilic or hydrophobic (therapeutic) molecules can be incorporated into electrospun fibers and (f) the fiber's surface can be easily functionalized which may be attractive to attach *e.g.* antibodies, peptides or any other biological materials.

1.2 The process of electrospinning

A typical electrospinning setup consists of three major components, being (a) a high voltage power supply (typically 5 to 50 kV), (b) a spinneret (*e.g.* a syringe with needle) and (c) a grounded collector (like a sheet of aluminium)¹³ (Fig. 2a).

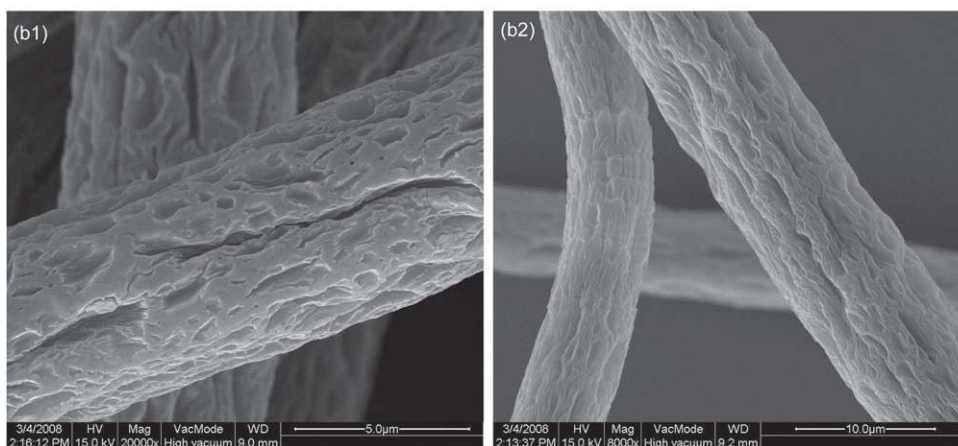
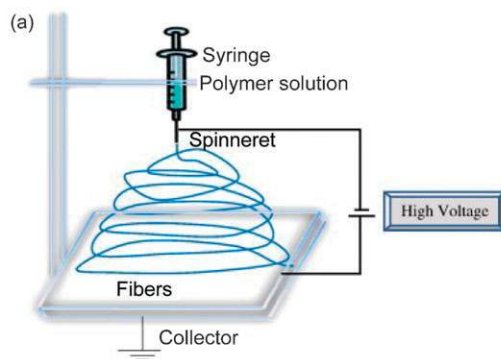


Fig. 2 (a) A laboratory setup for an electrospinning experiment with a perpendicular arrangement of the electrodes. (Reprinted from ref. 13 with permission. Copyright Elsevier.) (b) SEM images of polystyrene electrospun fibers, showing typical porous fibers.

More advanced setups enabling the production of *e.g.* oriented fibers or core-shell fibers consist of the same setup, with some minor alterations such as the use of, respectively, a rotating drum collector (to make aligned fibers) or two coaxial capillaries.¹⁴ The positive electrode of the high voltage power supply connects to the capillary, the collector connects to the ground.¹³ Due to surface tension, a droplet of the (polymer) solution is formed at the tip of the needle. Applying the electric field induces charges on the droplet surface, leading to a force directly opposite to the surface tension. By increasing the intensity of the electric field, the number of surface charges increases until the resulting force overcomes the surface tension of the liquid. This is typically seen by an elongation of the droplet into a so-called Taylor cone followed by a jet of (polymer) solution which is ejected from the tip of the Taylor cone. The trajectory of the ejected fiber can be controlled by the electric field and will be routed towards the grounded collector. During this passage in air, the remaining solvent evaporates, finally leaving the bare charged polymer fibers on the collector (Fig. 2).

1.3 Parameters which influence electrospinning

The wide variety in different types of polymers and solvents used for electrospinning renders it impossible to define “gold-standard” parameters applicable to every process. For each polymer solution (polymer and solvent), different electrospinning parameters can lead to fibers with very different characteristics.¹² Fig. 3a overviews the “global effects” on

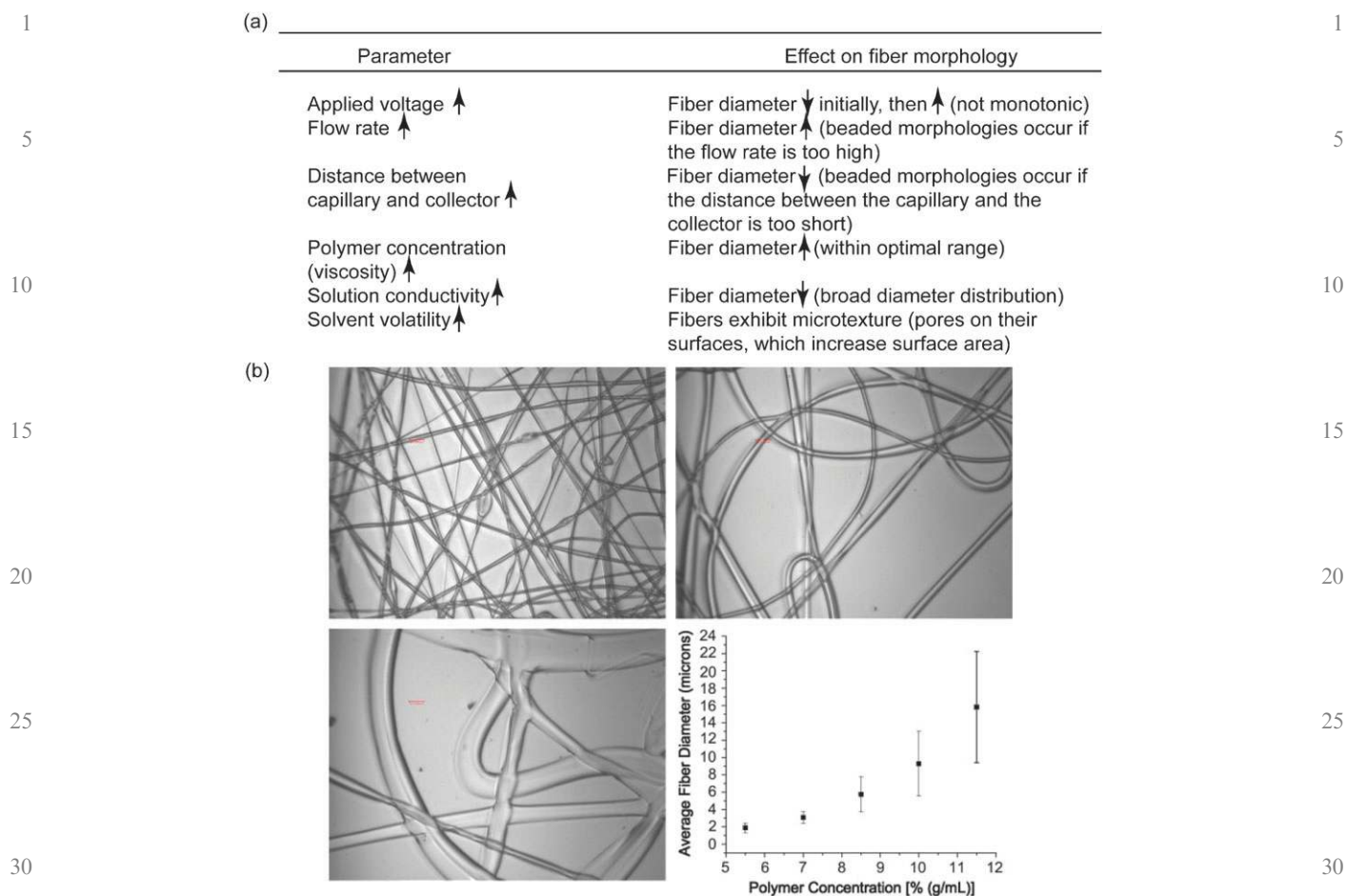


Fig. 3 (a) Effects of electrospinning parameters on fiber morphology (reprinted from ref. 12 with permission. Copyright Elsevier). (b) Effect of polymer concentration on fiber diameter. Fibers were electrospun from solutions containing varying concentrations of poly(ethylene-co-vinyl alcohol) in 70 : 30 (v : v) 2-propanol: DI water. Top left: fibers electrospun from a 5.5% (g mL^{-1}) solution. Top right: fibers electrospun from an 8.5% (g mL^{-1}) solution. Bottom left: fibers electrospun from an 11.5% (g mL^{-1}) solution. The following processing parameters were used for all experiments: applied voltage: 20 kV (+ polarity), flow rate: 3 mL h^{-1} , capillary-collector distance: approximately 25 cm. In the bottom right panel the relationship between the average fiber diameter and the polymer concentration is given. Note that the mean fiber diameter increases monotonically with increasing polymer concentration. Additionally, it is evident that ribbon-like fibers are formed at higher concentrations (11.5%), which indicates incomplete polymer drying. (Error bars represent the standard deviation.) (Reprinted from ref. 12 with permission. Copyright Elsevier.)

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the fibers one can expect by changing the composition of the polymer solutions and processing parameters.

The applied electric field strength plays important roles in the morphology of the electrospun fibers. For electrospinning, the ionic conduction of charge in the polymer solution (= electric current) is usually small enough to be neglected.¹⁵ The only way by which charge can be transported is by polymer flow through the needle. Thus, an increase in electric current will be associated with increased flow rates, which can lead to beaded morphologies.¹²

Varying the flow rate of the polymer solution will have similar effects on fiber morphology, but can also affect fiber porosity. For higher flow rates, the diameter and pore size increase accordingly.¹⁶ For very high flow rates, fibers may not dry completely before reaching the collector, which may result in beaded morphologies.¹²

Beaded morphologies caused by inadequate fiber drying can also occur when the distance between the capillary and the

collector is too short.¹⁶ When this distance enlarges, the diameter of the fibers will decrease, although this effect is generally rather limited compared to the effect of the other parameters.¹⁷

The concentration of polymer is very important as this will determine whether fibers can be electrospun or not. If the solution is too dilute, the surface tension will make the polymer break up into droplets before reaching the collector. A high polymer concentration will affect the viscosity of the solution and may make it impossible to get a gradual flow within the capillary and will induce beaded morphologies. All polymers therefore have an optimal concentration range in which they can be electrospun. Within this optimal range, higher polymer concentrations lead to increased fiber diameters (see Fig. 3b).¹²

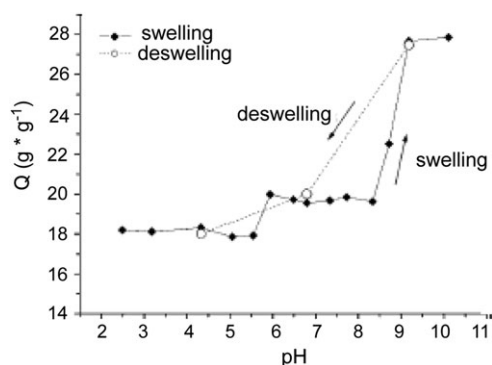
The conductivity of the solution can affect the fiber diameter distribution. Highly conductive solutions will be extremely unstable in the presence of strong electric fields, leading to

1 dramatic bending instabilities and a broad diameter distribution.
More stable fibers can be produced using semi-conducting and
insulating liquids.¹⁸

2 The volatility of the solvent is very critical as it will
3 determine whether fibers can be electrospun and will affect
4 fiber porosity. Preferably, quite volatile solvents are used
5 during transfer from the capillary to the collector, all solvent
6 has to evaporate in order to get nice fibers with similar
7 morphologies. Very volatile solvents will lead to a saturation
8 of the atmosphere immediately surrounding the fiber with
9 vapor and hereby facilitate the development of a porous
10 surface morphology.¹²

15 2. Stimuli-responsive electrospun fibers

16 One should realize that the response rate of a material upon
17 applying one or another stimulus is strongly governed by the
18 transfer rate of the stimulus into the material. The response
19 (*e.g.* swelling) rate of a stimulus-sensitive object is therefore
20 mostly dependent on a diffusion process^{1,19} and thus inversely
21 correlated to its thickness.²⁰ A too slow response may limit its
22 application. Due to “geometry reasons” electrospun fibers,
23 with a submicrometre diameter and a high surface to volume
24 ratio, which facilitates the transfer of the stimulus to the
25 whole fiber, could lead to materials with a fast response. As
26 an example, ultrafine hydrogel nanofibers were found to have
27 a faster response rate than monolithic hydrogel films.²¹
28 Furthermore, the high porosity of electrospun fibers has been

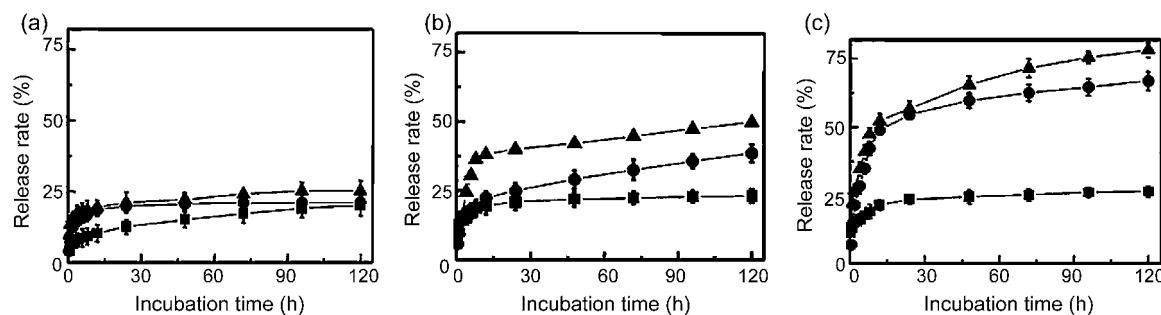


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35
40
45 **Fig. 4** Water absorption by SMA-Na-DEG/cellulose hydrogel nanofibers (gram water per gram nanofiber) as a function of the pH of the buffer. (Reprinted from ref. 20 with permission from Society of Chemical Industry.)

1 found to enhance the mass transport of *e.g.* ions and chemicals
2 from a surrounding solution to enzymes and cells embedded
3 within the hydrogel.²²

5 2.1 pH-responsive electrospun fibers

6 pH-sensitive polymers have gained a lot of attention for drug
7 delivery purposes as they may allow a pH controlled release of
8 therapeutic compounds.²³ Polymers containing carboxylic
9 acids or amine groups are useful for such purposes as a change
10 in pH results in protonation or deprotonation and associated
11 changes in hydrophilicity. Alternatively, polymers composed
12 of acid-labile bonds (such as acetal or hydrazone groups) are
13 attractive to induce drug release specifically at low pH. Cao
14 *et al.*²⁰ described the preparation of pH-sensitive crosslinked
15 poly[styrene-*co*-(maleic sodium anhydride)] (SMA) and
16 SMA-cellulose acetate composite nanofibers, which were then
17 crosslinked at elevated temperature in the presence of
18 diethylene glycol, resulting in hydrogel nanofibers. Compared
19 with classical cast hydrogels, these fibers displayed better
20 mechanical strength and a pH-dependent swelling when
21 immersed in water. The latter was due to a pH-dependent
22 degree of water absorption (being 18.0 g g⁻¹ at pH 2.5 and
23 28.0 g g⁻¹ at pH 9; Fig. 4). Qi *et al.*²⁴ described pH-sensitive
24 electrospun fibers based on *ortho* ester groups which are
25 suitable for drug release in mildly acidic conditions; these
26 fibers are stable at pH 7.4, but degrade at lower pH
27 (5.6 and 4.0) which accelerates the release of *e.g.* entrapped
28 paracetamol, used as a model drug. In a different study,
29 Cui *et al.*²⁵ showed that introducing pH-sensitive acetal
30 groups (which hydrolyse at acidic pH) into the backbone of
31 poly(D,L-lactide)-poly(ethylene glycol) accelerated the release
32 of paracetamol from fibers made of this co-polymer (Fig. 5).
33 Clearly, the concept of pH triggered release from electrospun
34 fibers has been shown experimentally *in vitro*. Though, one
35 could wonder for which specific treatments applying
36 pH-sensitive drug-loaded electrospun fibers in the body could
37 be attractive. As an example, a local low(er) pH has been
38 reported to exist *e.g.* in some endosomal compartments of
39 cells,²⁶ in tumors²⁷ and in inflamed tissues.²⁸ pH-triggered
40 drug release from nanoparticles in such acidic environments
41 has been studied.²⁹⁻³¹ To our knowledge there are so far no
42 reports which clearly indicate where pH-triggered drug release
43 in these acidic regions from (cylindrical) electrospun fibers
44 would be an advantage over drug release from spherical
45 particles. This remains also unclear to us.



50
55 **Fig. 5** Release of paracetamol from pH-sensitive PELA-10 (a), PBELA-5 (b) and PBELA-10 (c) acid-labile electrospun fibers in pH 7.4 (■), 5.5 (●) and 4.0 (▲) buffer solutions at 37 °C. (Reprinted from ref. 25 with permission. Copyright Elsevier.)

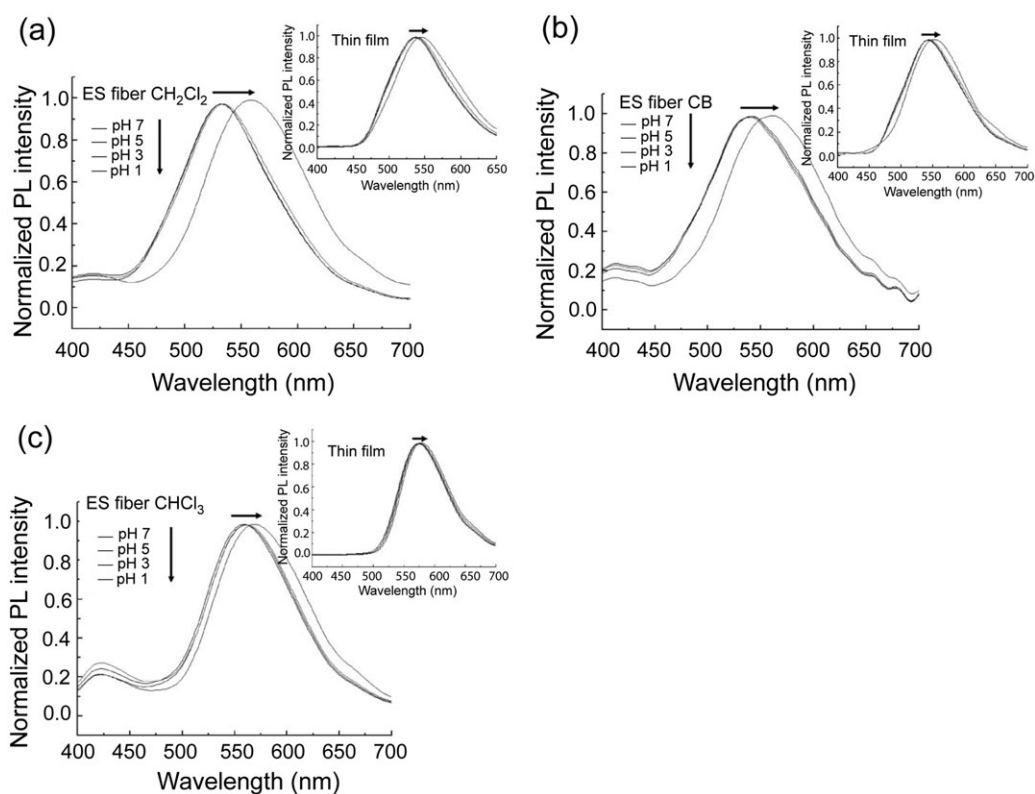


Fig. 6 The pH sensing characteristics of photoluminescence spectra of PPQ-*b*-PS/PS blend electrospun fibers prepared from the solvents CH₂Cl₂ (a), chlorobenzene (CB) (b) and CHCl₃ (c), indicating a clear red-shifting of the photoluminescence spectra when the pH drops from 7 to 1. The insets show cast thin films under identical conditions. (Reprinted from ref. 32 Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

pH-responsive electrospun fibers have been reported as pH sensors in bioreactors *e.g.* to monitor acidification of culture media. Luminescent electrospun fibers would provide an easy, cheap and sensitive method for continuous pH monitoring of culture media and minimize the risk of contamination compared to repeated pH electrode exposures. In this regard, Kuo *et al.*³² designed electrospun fibers from blends of poly(phenylquinoline)-*block*-polystyrene (PPQ-*b*-PS) and polystyrene (PS). Within the fibers, multiple domains of aggregated PPQ-*b*-PS were observed, ranging in size between 1 and 4 μm, depending on the solvent used. For fibers spun in CH₂Cl₂ the emission maxima varied from 532 nm to 560 nm going from pH 7 to pH 1 (Fig. 6), the pH-induced shift in the spectra being caused by protonation of the PPQ moiety. The use of electrospun fibers rather than nanoparticles is of great importance for the functionality of these sensors as the high surface over volume ratio makes the fibers ideally suitable for sensory applications. Of further interest is the fact that the process of electrospinning itself can lead to polymeric fibers with distinct optoelectronic and photophysical properties, which are clearly different to those of fibers prepared from the same polymer but by a different method.³³

Attractive pH-sensitive electrospun fibrous membranes were reported by Jin and Hsieh.²¹ These authors made use of aqueous mixtures of poly(vinyl alcohol) (PVA) and poly(acrylic acid) (PAA) to make, respectively, fiber webs by electrospinning and films by solution casting; the fiber webs

and films were then crosslinked by heat-induced esterification. When these fiber webs and films were exposed to buffers with pH ranging from 2 to 10 they became thicker and their surface expanded. For the PVA/PAA films, the surface expansion and the increase in thickness were comparable (3-fold upon a pH change from 2 to 10), whereas for the electrospun PVA/PAA fiber webs the increase in thickness (4-fold) was much more pronounced than the surface expansion (2-fold). The latter is due to the asymmetric distribution of the fibers in the electrospun webs. This unique feature may be of use in applications where asymmetric mechanical transformation is of interest, such as in the development of artificial muscles.³⁴

2.2 Temperature-responsive electrospun fibers

Thermo-responsive polymers have been paid considerable attention due to their potential applications in sensors, actuators, drug delivery systems and cell cultures.^{35–37} Thermo-responsive poly(*N*-isopropylacrylamide) (poly(NIPA)), with a lower critical solution temperature (LCST) in the range of 31–35 °C, has been well characterized over the past 30 years. Below the LCST, the polymer easily dissolves in water while at temperatures above the LCST, it becomes insoluble and precipitates out of aqueous solutions.

Rockwood *et al.*³⁸ described the preparation of three-dimensional electrospun poly(NIPA) fibrous mats and showed by Raman spectroscopy and FTIR that the electrospinning

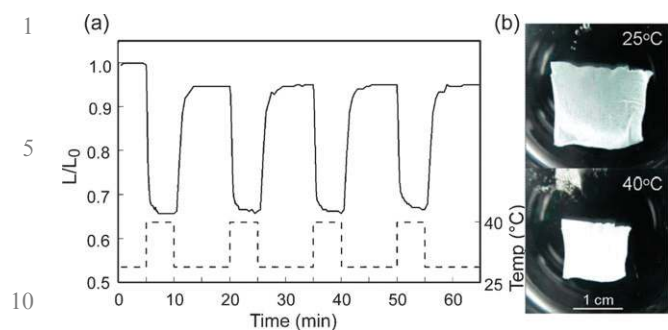


Fig. 7 (a) Temperature-dependent deswelling and swelling of poly(NIPA-*co*-SA) nanofiber mats (2 cm × 2 cm × 20 μm) in pure water (between 25 and 40 °C; L/L_0 is the length of the fiber mat expressed as relative to the original length at 25 °C); (b) shows representative photomicrographs of the fibers at 25 °C (top) and 40 °C (bottom). (Reprinted from ref. 39 with permission of American Chemical Society.)

process did not alter the structure of the polymer. Continuing on these observations, Okuzaki *et al.*³⁹ prepared poly(*N*-isopropylacrylamide-*co*-stearyl acrylate) (poly(NIPA-*co*-SA)) electrospun nanofiber mats having an average diameter of 207 nm. Interestingly, as Fig. 7a and b illustrate, poly(NIPA-*co*-SA) nanofiber mats exhibit rapid (and reversible) swelling when temperature drops from 40 °C to 25 °C. Importantly, in contrast to bulk poly(NIPA-*co*-SA) gels, the swelling rate of the nanofiber mats was found to be one order of magnitude higher due to the larger surface and high porosity of the fibers which promote the diffusion of water into the mats. As the LCST of polymers can be varied by carefully selecting the alkyl chain-length of the hydrophobic monomers, this might open up a broad window of applications for temperature-sensitive nanofiber mats.

There is an interest in materials with surfaces having a “controllable” wettability, being super hydrophobic under one condition and super hydrophilic under other conditions. Such materials would find many practical applications as they would be self-cleaning⁴⁰ or enable well-controllable drug delivery.⁴¹ Super hydrophobic surfaces would also minimize oxidation, contamination or current conduction because of the small contact area with water.⁴² In this regard, Wang *et al.*⁴³ prepared electrospun responsive pNIPA/polystyrene (pNIPA/PS) composite nanofiber mats. By altering the concentration of the polymers, the wettability of the fibers could be easily fine-tuned. Optimal temperature-sensitive wettability was achieved for fibers spun from a pNIPA/PS/THF solution (2 : 10 : 90; w : w : w). As Fig. 8 shows, the water contact angle of the fiber mats increased enormously upon heating the mats from 20 to 50 °C. In a similar study, Gu *et al.*⁴⁴ produced pNIPA/poly-L-lactide (pNIPA-PLLA) composite nanofibers with a temperature-dependent wettability, where PLLA was added to overcome the relatively poor electrospinnability of pNIPA. While PLLA nanofibrous films had (temperature independent) water contact angles of about 133°, the addition of pNIPA rendered the fibers a temperature-dependent wettability, with contact angles of less than 20° at room temperature and higher than 130° at 50 °C.

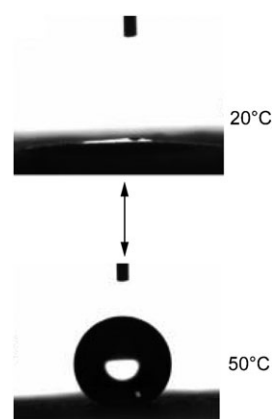


Fig. 8 Shape of a water droplet on an electrospun pNIPAAm/PS composite mat showing its thermoresponsive properties; the fibers are hydrophilic at low temperature (20 °C) while hydrophobic at elevated temperature (50 °C). (Reprinted from ref. 43 Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

The temperature-dependent solubility of pNIPA has been further exploited by Fu *et al.*⁴⁵ who developed a method to coat electrospun fibers, made from block copolymers of 4-divinylbenzene chloride (VBC) and glycidyl methacrylate (GMA), with a temperature-responsive surface. Electrospun PVBC-*b*-PGMA fibers were exposed to sodium azide, which induced cross-linking and bestowed the surface of the fibers with azido groups. Alkyne-terminated pNIPA could react with these azido groups by click chemistry, leading to pNIPA brushes on the surface of the PVBC-*b*-PGMA fibers. These fibers were shown to exhibit a reversible, temperature-dependent surface wettability, with water contact angles of 140° and 30° at, respectively, 45 °C and 20 °C. The latter approach of surface-coating the fibers was chosen to circumvent the rather poor electrospinnability of pNIPA which generally requires the use of well-balanced composite mixtures and specific solvents.

Smart hydrogels display a reversible swelling in response to external stimuli, such as pH¹⁶ or temperature. As outlined above, the rate of swelling is a diffusion-controlled process, which is therefore inversely correlated with the thickness of the gel. By means of electrospinning, Wang *et al.*⁴⁶ prepared fibrous porous membranes composed of poly(NIPA-*co*-acrylic acid) (pNIPA-*co*-AAc) and poly(NIPA-*co*-hydroxyethyl methacrylate) (pNIPA-*co*-HEMA) in order to try to increase the response rate of the polymers upon exposure to different temperatures. After cross-linking at elevated temperatures, the effect of ionization (of the carboxyl groups in AAc, by adding sodium hydroxide) on the response rate of the electrospun fibers was investigated. It was observed that ionization significantly fastened the swelling and deswelling rates of the fibers at temperatures below and above the LCST of the fibers, respectively. Equilibria were reached after 30–60 s and 90–200 s for, respectively, swelling and deswelling, in contrast to non-ionized fibers which reached equilibria at 5 min and 3–5 min, respectively. The rapid response rates may make such materials highly interesting for *e.g.* the controlled release of compounds or for biomolecular separation purposes.

1 2.3 Magnetic field-responsive electrospun fibers

There has been a substantial interest in the potential of magnetic materials for diverse types of biomedical applications.⁴⁷

5 Examples include magnetic targeting of drugs encapsulated in magnetic responsive carriers to tissues, magnetic heating of (e.g. cancerous) tissues (magnetic hyperthermia)^{48,49} and time controlled release of drugs from magnetic responsive polymer hydrogels.⁵⁰ Bulk ferromagnetic materials, such as magnetite, consist of multiple magnetic domains (Weiss domains) which are all randomly oriented, leading to zero net magnetization. When exposed to an external magnetic field, these domains will reorient themselves and align with this field, leading to a positive net magnetization. As the different clusters are magnetically linked, removal of the external magnetic field will bestow the bulk material with a remnant magnetization.⁵¹

This residual magnetization hinders most biomedical applications, and a lot of effort has been put in developing materials which exhibit net magnetic moments in the same order as ferromagnetic materials but which do not exhibit any remnant magnetization in the absence of an external field. When ferromagnetic materials are decreased in size, they will eventually become smaller than the individual Weiss domains they are composed of (for magnetite in the order of 50 nm diameter).⁵¹ As these small particles, termed superparamagnetic, no longer contain multiple magnetic domains, no remnant magnetization is observed whereas their magnetic moment is the same as that of their bulk ferromagnetic material.

Such superparamagnetic particles have also been used to create magnetically-responsive electrospun fibers for various applications. Wang *et al.*⁵² described poly(acrylic acid)-coated magnetite particles (7.5 ± 2.9 nm core diameter, 25 nm hydrodynamic diameter) which were suspended in polyethylene oxide (PEO) or polyvinyl alcohol (PVA) for electrospinning. PEO fibers of 400 ± 80 nm diameter and 28% (wt%) magnetite, and PVA fibers of 320 ± 40 nm diameter and 8% (wt%) magnetite were produced. The fibers were found to exhibit superparamagnetic properties, showing a deflection of the fiber mats towards an external magnet. The extent of this deflection was correlated with the strength of the magnetic field. In a similar study, Gupta *et al.*⁵³ used superparamagnetic MnZnFe-Ni particles (14 nm core diameter) which could be embedded at different ratios (6, 11, 18 or 26 wt%) in Estane[®] fibers, a commercially available polyester-based segmented polyurethane. Fibers with a diameter of 300 – 50 nm were produced which exhibit superparamagnetic behavior without remnant magnetization.

Graeser *et al.*⁵⁴ prepared pure metal fibers using cobalt or iron nitrate as metal precursors which were dissolved at high concentration in poly(vinyl butyral) (PVB). After electrospinning, the polymer matrix was degraded and the metal salts were reduced, leading eventually to pure cobalt or iron fibers with an average diameter of about 150 nm. Using a fast rotating drum as the collector, the highly charged fibers could easily be aligned. Upon arranging the fibers in mats of 5 mm by 5 mm, the fibers were also found to exhibit superparamagnetic properties, with saturation magnetization of 57 emu g^{-1} for the parallel fibers and 18 emu g^{-1} for perpendicular fibers. In a different study of the same group, cobalt nanoparticles

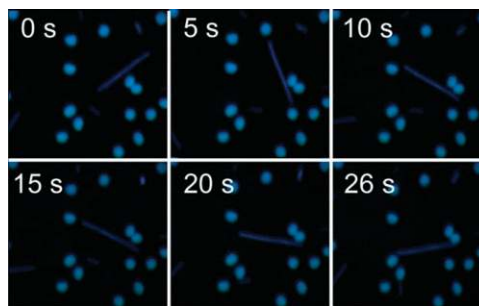


Fig. 9 Movement of magnetic Co/P(MMA-*c*-VA) composite fibers dispersed in a water droplet which contains stained nuclei of hippocampal cells (blue spots); the fibers were manipulated manually by a ferromagnet. (Reprinted from ref. 55 Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

(9 nm diameter; 25 wt%) were dispersed in the fluorescent copolymer methylmethacrylate (MMA) and 9-vinylanthracene (Anth) leading to pMMA-*c*-VA (30 wt%) fibers of 1–3 μm diameter which were collected on a rotating drum collector and then cut into pieces of 50–100 μm length.⁵⁵ Using an external magnetic field, dispersed fibers could undergo translational movement in water by moving the magnet horizontally, or fibers could be rotated by rotating the external magnet. The high control over fiber movement even allowed the researchers to position fibers so that a single fiber connected two primary hippocampal neurons within less than 30 seconds (Fig. 9). Such fibers could be used as excellent scaffolds for drug delivery or as potential self-building nerve bridges to overcome neuronal degeneration in neurodegenerative diseases by allowing efficient cell-cell contact and enabling enzyme delivery or transmission of small currents. Combining the fibers with carbon nanotubes might offer an exciting way to electrically stimulate the nerve cells and aid neural regeneration.⁵⁶ Such applications would all be possible owing to the typical geometric confinements of electrospun fibers and would be near impossible to achieve by commonly used magnetic nanoparticles. The high loading capacity of electrospun fibers for magnetic nanoparticles would further augment their magnetic properties and thus facilitate magnetic guidance of the fibers or possibly lead to highly efficient magnetic hyperthermia setups.

2.4 Photo/optical-responsive electrospun fibers

The high ratio of surface over volume of electrospun nanofibers makes them ideal candidates for use as chemical sensors, as it is believed that the sensitivity of a sensor correlates with the surface to volume ratio. Compared to thin films, the surface area of electrospun nanofiber mats can be one to two orders of magnitude higher.⁵⁷

The first study on electrospun fibers for the (optical) sensing of metal ions and 2,4-dinitrotoluene (DNT) was reported in 2002.⁵⁸ Fluorescent poly(acrylic acid)-poly(pyrene methanol) (PAA-PM) was used as the matrix polymer for electrospinning, mixed with cross-linkable polyurethane latex. When in the presence of Fe^{3+} , Hg^{2+} or DNT, fluorescence was efficiently quenched by electron-deficient analytes and fluorescence intensity inversely correlated with the analyte

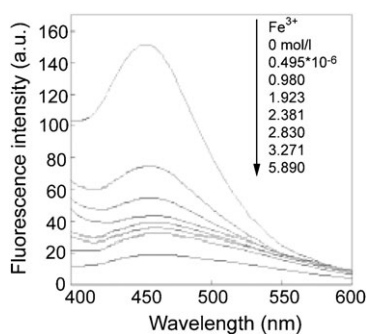


Fig. 10 Fluorescence emission spectra of electrospun membranes as a function of the Fe^{3+} concentration in the medium. (Reprinted from ref. 58 with permission of American Chemical Society.)

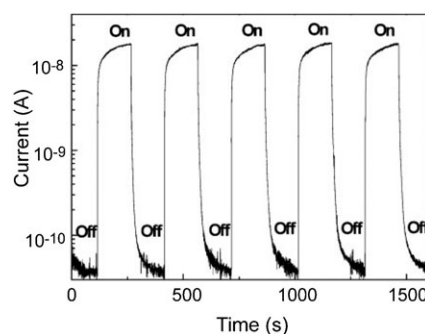


Fig. 11 Alterations in conductivity of a GaN nanofiber upon pulsed illumination with UV light. (Reprinted from ref. 64 Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

concentration (Fig. 10). Using a Stern–Volmer bimolecular quenching relationship, the analyte concentration could be efficiently determined. Interestingly, the Stern–Volmer constants were two to three orders of magnitude higher than those obtained using classical thin film sensors,⁵⁹ indicating the superior sensitivity of the nanofiber sensors to be in the range of a few parts per billion (ppb). The same group also reported the production of electrospun cellulose acetate (CA) nanofibrous membranes which were surface decorated with poly[2-(3-thienyl) ethanol butoxy carbonyl-methyl urethane] (H-PURET), a fluorescent probe.⁶⁰ Fiber diameters ranged from 100 to 400 nm and fluorescence signals could be efficiently quenched when the fibers were exposed to only ppb amounts of electron acceptor methyl viologen or electron-transfer protein cytochrome *c*. The detection of explosive agents, such as DNT, by electrospun fibers has been further investigated by Long *et al.*⁶¹ who developed a novel type of fluorescent conjugated polymer which could be efficiently electrospun without any significant aggregation and associated self-quenching of the fluorophores, being a major bottleneck for many types of fluorescent conjugated polymers. The fibers with a diameter of 300–400 nm displayed a uniform morphology and were found to be efficiently quenched in the presence of trace amount of DNT. Compared with the cast film, which showed only 5% fluorescence quenching in 1 h time when exposed to DNT vapor, nanofibrous films displayed 50% fluorescence quenching in the same time period. Moreover, the use of sodium dodecyl sulfate as a pore-forming agent in the nanofibrous films further increased the interaction of DNT with the fluorescent probe, leading to even 75% of fluorescence quenching after 1 h exposure. Taken together, these data highlight the importance of the high surface to volume ratio and put forward electrospun fibers as highly sensitive optical sensors thanks to an efficient interaction of the analyte with the fluorescent probe. Moreover, fluorescent quantum dots, which possess high quantum yield and which are far more resistant to fluorescence bleaching and therefore have a much longer fluorescence lifetime than organic fluorophores, have also been described to be homogeneously distributed in polymer nanofibers while maintaining their characteristic optical features.⁶² This offers a wide variety of potential novel applications for these optical sensors with even higher sensitivity.

Where the previous reports all deal with chemical sensors showing an optical output, electrospun fibers can also be used as photodetectors. In this regard, group III N alloys, particularly GaN, have demonstrated to possess enormous potential to be used as nanosized field-effect transistors (FETs) or ultraviolet (UV) photo-detectors.⁶³ Using electrospinning, extremely long (up to 1 cm) but very thin (40 nm diameter) GaN nanofibers could be produced, using poly(vinyl pyrrolidone) (PVP) as the matrix polymer.⁶⁴ When exposed to UV light, the conductance of these semiconductors greatly increased, resulting in an electric signal as output for UV detection. The conductance of the electrospun GaN nanowires increased nearly 830 times which is over 10-fold higher than for GaN nanowires produced by classical chemical vapour deposition.⁶⁵ These electrospun fibers were superior to classically produced GaN nanowires in terms of increased sensitivity, response rate and reversibility (Fig. 11).

Photoresponsive electrospun nanofibers may be an attractive as well as triggered drug delivery system. To this end, PVBC-*b*-PGMA fibers were electrospun (500 nm diameter) after which azido groups were put on the surface by exposing the fibers to sodium azide, as explained above.⁶⁶ By means of click chemistry, azobenzene molecules were then placed on the surface, which can undergo a *trans* to *cis* configuration change when exposed to UV light. As a model drug, the anticancer compound 5-fluorouracil was used, which is also available as a α -cyclodextrin conjugated prodrug. Interestingly, α -cyclodextrin can efficiently bind azobenzene in its *trans* configuration but cannot bind when azobenzene is in its *cis* configuration. As such, exposure of the fibers to UV light led to a well-controllable release of 5-fluorouracil (Fig. 12). Note that there was no drug release at all when the fibers were immersed in water for 1 h in the dark, while maximal drug release was already observed after 30 min of UV exposure. By exposing the fibers to several ‘UV light intervals’, interspersed by periods when the fibers were placed in the dark, it was clearly shown that drug release only occurred upon UV exposure. This photocontrolled on–off system is promising as many α -cyclodextrin based prodrugs are available. This drug delivery concept should be further tested on cell cultures, however. Further optimization is required to translate this technology into an *in vivo* setting, taking into account the limited penetration depth of UV light in human tissue,⁶³ the damage of biological tissues by UV irradiation⁶⁷ and the fact that several polymer

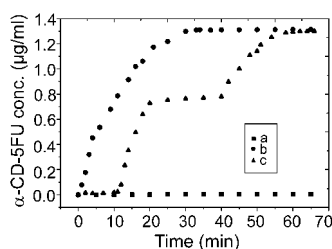


Fig. 12 Release of α -CD-5FU in water from CNFPVBC-*b*-PGMA-AB fiber mats with surface-loaded α -CD-5FU. The lower curve (■) shows the release in the dark; the upper curve (●) is the release upon continuous UV irradiation. The middle curve (▲) shows the release upon intermittent UV irradiation. (Reprinted from ref. 66 with permission of American Chemical Society.)

types cannot be used as they avidly absorb UV.⁶⁸ A possible alternative may lie in the use of near infrared-sensitive probes as it overcomes most of the problems associated with UV irradiation.⁶⁹

2.5 Chemical stimulus-responsive electrospun fibers

2.5.1 Humidity-responsive electrospun fibers.

Humidity nanosensors have been actively studied and find many applications in electronics, air conditioning and meteorological devices.⁷⁰ Polymeric humidity nanosensors undergo a change in electrical resistance and/or capacity when water absorbs inside the pores which are typically present in great numbers for electrospun polymers.⁷¹ The principle of humidity sensing using these nanoporous polymeric thin films is based on ionic conduction where the total impedance of the sensor is reduced in correlation with the amount of water absorbed.⁷² Previously, nanoporous materials based on polycarbonate or cellulose acetate were shown to enable the detection of water.⁷⁰ Furthermore, these materials did not undergo significant swelling, were mechanically more robust and led to more sensitive detection than materials such as ceramics or polyimide, which were classically employed for humidity sensing.⁷⁰ Logically, the higher surface over volume ratio of electrospun fibers could also enhance the extent of water absorption and therefore lead to a more sensitive detection system.

For humidity sensing, quartz crystal microbalances (QCM) have been used as sensitive humidity sensors.⁷³ Vogt *et al.*⁷⁴ reported on thin (PAA/PVA) polymer films which were coated onto the electrode of a QCM, leading to a stable but rather slow detection system. The sensitivity of such coated QCM system could be enhanced nearly 2-fold upon coating the electrode with composite PAA-PVA electrospun fibers compared with PAA/PVA films.⁷⁵

Alternatively, the QCM could also be avoided and electrospun fibers could be directly coupled to an electrode for humidity sensing. In this regard, lithium perchlorate (LiClO₄) doped-polyethylene oxide (PEO) were produced, leading to ionically conducting electrospun nanofibers.⁷⁶ Compared to cast thin films, the high porosity and high surface of the electrospun fibers led to a better sensitivity (when the % humidity was expressed against the measured resistivity, the slope of the curve for electrospun fibers was nearly 5 times as high as for cast films). The high humid sensitivity with fast response and recovery times of electrospun nanofibers could

be achieved with other materials. For instance, Li *et al.*⁷⁷ prepared a highly porous non-woven mat of PEO-polyaniline (PANI) composite fibers (250–500 nm diameter). The impedance changed from 6.3×10^6 to $2.5 \times 10^4 \Omega$ when the relative humidity increased from 22 to 97% with response and recovery times in the order of seconds. The rather high impedance of the fibers could further be efficiently reduced (nearly two orders of magnitude) by enhancing the contact between the fibers and the electrode, for instance by coating the electrode with poly(diallyldimethylammonium chloride), a commonly used polyelectrolyte.

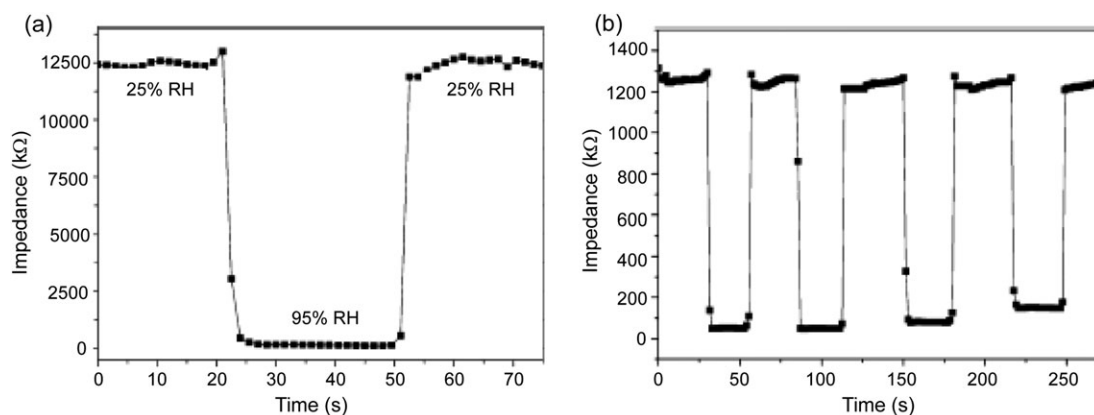
The high sensitivity and fast response rates of electrospun fibers were further exploited by Li and colleagues,⁷⁸ who developed lithium chloride (LiCl) doped titanium dioxide (TiO₂) nanofibers by electrospinning and calcination. This novel type of humidity sensor displayed impedance changes from 10^7 to $10^4 \Omega$ when humidity levels in air increased from 11 to 95%, indicating a highly sensitive device. Furthermore, the response rate (being 3 s for humidity changes from 11 to 95%) of 30% LiCl-doped TiO₂ nanofibers was extremely fast. The high sensitivity, reproducibility and extremely fast response time clearly outmatched all the common thin film polymeric humidity sensors.^{79,80}

These excellent features were also observed in separate studies, for instance by Zhang *et al.*⁸¹ who used Na⁺-doped ZnO nanofiber membranes and by Qi *et al.*⁸² who used KCl-doped TiO₂ nanofibers. A clear breakthrough was made by the same group in 2009 using KCl-doped ZnO electrospun nanofibers.⁷⁹ For 5.7 wt% KCl-doped ZnO fibers, having diameters of approximately 500 nm, very rapid response (2 s) and recovery times (1 s) could be achieved (Fig. 13). This enhanced response rate was likely due to the intrinsic characteristics of the materials used, with ZnO having excellent electrical and piezoelectrical properties and potassium ions which further augment the ionic conduction.

Taken together, the data above display the high potential of electrospun fibers for humidity sensing due to their fast response and recovery times, high stability and sensitivity. By carefully selecting the materials used, such as KCl-doped ZnO, very efficient humidity sensors can be produced and further achievements in terms of sensitivity can be made by enhancing the contact between the fibers and the electrode by coating the latter with a polyelectrolyte.

2.5.2 Glucose-responsive electrospun fibers.

Glucose-sensors could have a great influence on life comfort of patients with diabetes mellitus if a fast, sensitive and stable sensor could be found which can in real time measure blood glucose levels. To this end, amperometric glucose sensors are actively studied, which contain immobilized enzymes, such as glucose oxidase or glucose dehydrogenase, which allow a direct and rapid electron transfer to the electrode surface, using, for instance, an enzyme-immobilized nitrocellulose strip.⁸⁴ Again, the high surface to volume ratio of electrospun fibers is attractive for a more sensitive detection as the larger surface allows for more enzyme units to be immobilized per unit mass of polymer. This was clearly shown in the work by Aussawasathien *et al.*⁷⁶ who produced camphorsulfonic acid (HCSA) doped-polyaniline (PANI)/PS copolymer electrospun



15 **Fig. 13** Impedance of KCl-doped ZnO nanofibers exposed to different humidity levels after (a) one cycle and (b) four cycles of exposure to 15
25–95% humidity. (Reprinted from ref. 83 with permission. Copyright Elsevier.)

nanofibers onto which glucose oxidase was surface-immobilized. For films exposed to glucose concentrations between 0 and 10 mM, a current of 0 to 2 $\mu\text{A g}^{-1}$ polymer was noted, whereas for fibers which were treated identically, currents from 0 to 35 $\mu\text{A g}^{-1}$ polymer were found, indicating a near 16-fold higher detection signal in case fibers were used. This clearly indicates the potential of the fibers for sensitive detection of glucose within a clinically relevant range (*i.e.* 3.6 to 5.8 mM glucose).

Although the higher sensitivity of such fiber based glucose sensors is a great improvement, sensors equipped with enzymes suffer from an intrinsic disadvantage being the denaturation of the enzymes which limits the stability of the sensor. To overcome this, Manesh *et al.*⁸⁵ proposed an interesting enzyme-free alternative in the form of boronic acid-containing electrospun fibers. An electrospun nanofibrous membrane, based on poly(vinylidene fluoride) (PVdF) and boronate-containing poly(aminophenylboronic acid) (PAPBA), was produced. The electrospinning process led to highly uniform fibers with an average diameter of approximately 150 nm. Boronate groups, as present in PAPBA, are known to complex with saccharides, enabling the sensitive detection of glucose (currents from 0 to 30 μA were noted for glucose concentrations ranging between 0 and 15 mM). The response was clearly linear over the whole concentration range tested and the response time was less than 6 s. Interestingly, the selectivity of the fibers for glucose over other saccharides could be achieved by using fibers which contained crown ether having the functional group 4-acryloylamidobenzo-15-crown 5. With these fibers, the selectivity for glucose was very high as galactose, mannose, fructose and maltose led to only 0.6%, 1.2%, 2.9% and 2.1% of the current response relative to that of glucose (when all saccharides were incubated together, each at a 1 mM concentration). Moreover, more than 90% of the original activity of the sensor was retained after 50 days, indicating the high stability of the sensor and its potential use for longer-term applications.

2.5.3 Protein-responsive electrospun fibers. The accurate and sensitive detection of proteins is of primordial importance in many biomedical research applications, such as *e.g.* the detection of mutant proteins associated with

neurodegenerative diseases like Alzheimer's, Huntington's or Parkinson's disease.^{86,87} To this end, a lot of effort is put in optimizing the sensitivity of protein detection, *e.g.* by developing novel staining techniques for Western blots⁸⁸ or by introducing completely new detection methods based on, as an example, gold nanoparticles.⁸⁹ These new techniques still suffer from important drawbacks in terms of limited sensitivity, poor linearity, or low ability for high-throughput analysis. Electrospun poly(dimethylsiloxane) (PDMS)/PMMA nanofibrous membranes were already shown to increase the sensitivity of protein detection, leading to a 32-fold enhancement of the detection limit compared to cast nitrocellulose membranes.⁹⁰ To date, quantitative protein detection is still mostly done by enzyme-linked immunosorbent assays (ELISA), where the target protein is caught by an immobilized enzyme and then detected by a secondary antibody. As the sensitivity of detection correlates with the availability of immobilized antibodies, a higher surface over volume ratio might significantly increase the detection limits. Tsou *et al.*⁹¹ fabricated silica-coated polyvinylpyrrolidone electrospun fibers with an average diameter of 100 nm which were ordered in a 1.3 cm by 1.3 cm fibrous membrane. As Fig. 14a shows, membranes were then coated with primary mouse antibody (protein B) or with bovine serum albumin (protein A) after which the secondary detection antibody, specific for protein B (protein C) was applied. Compared with conventional polystyrene ELISA well plates, the sensitivity could be strongly increased, up to 32-fold. Furthermore, in terms of duration, the fiber-based assay could be completed in 1 hour without any loss of sensitivity compared with 24 h needed for the conventional ELISA assay. These great improvements in sensitivity and short reaction time, just due to the higher surface over volume ratio of fibers compared with ELISA well plates, are attractive features for the development of accurate, low-cost, sensitive, high-throughput protein assays.

2.5.4 Gas-responsive electrospun fibers. Sensitive detection of explosive or toxic gases is an area of active research.^{92,93} In terms of sensitivity and speed of detection, sensors based on carbon nanotubes and semiconducting nanowires^{79,94} are far more efficient than conventional sensors based on semiconducting metal oxides ordered in thin films or thick mesoporous layers.

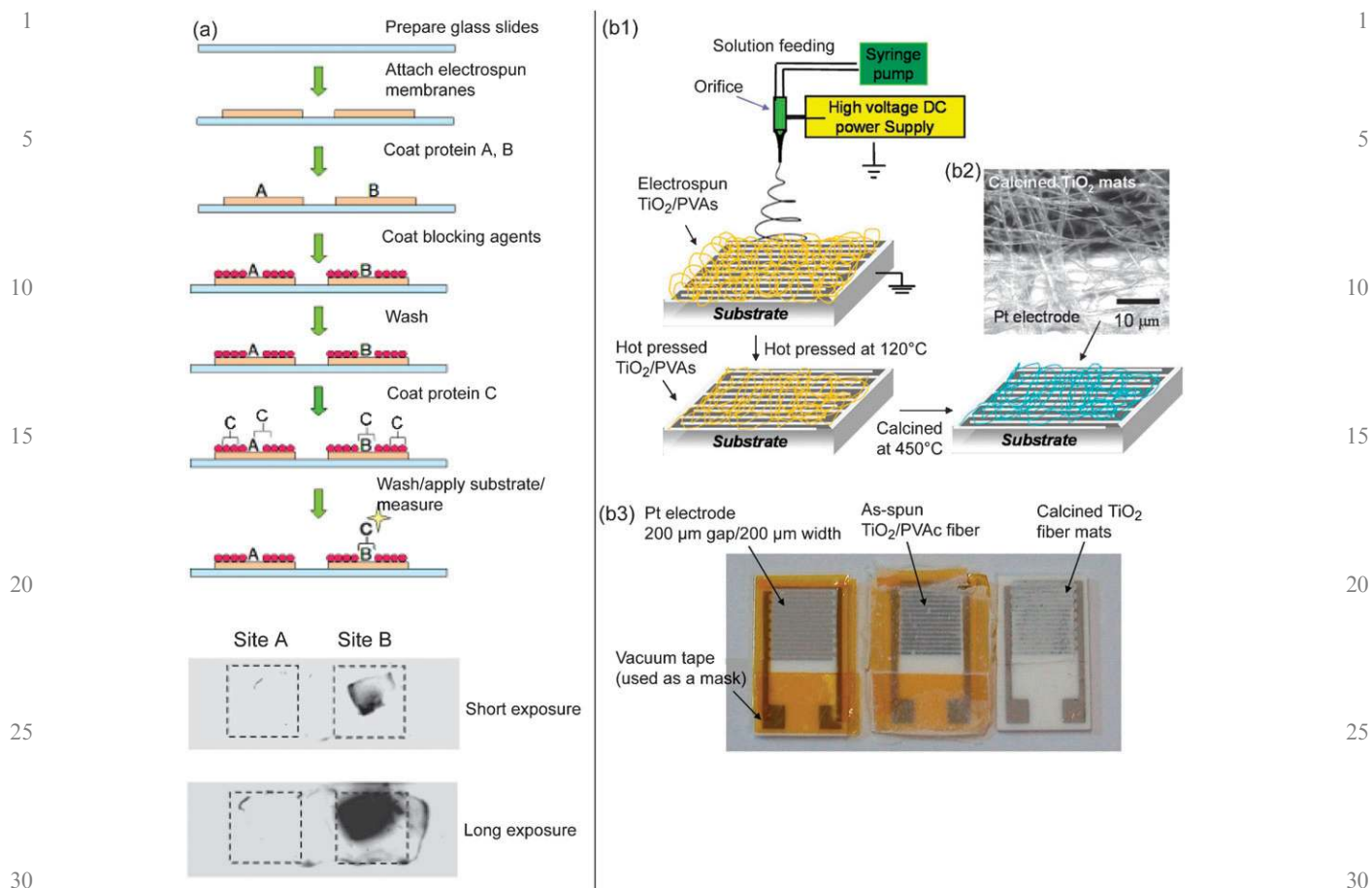


Fig. 14 (a) Procedure for the protein-attachment test for electrospun silica nanofiber membranes and the corresponding X-ray photos after a 10 s short exposure and a 2 min long exposure to X-rays. Proteins A, B, and C denote BSA, monoclonal mouse anti-FLAG M2 antibody and goat anti-mouse HRP. (Reprinted from ref. 87 with permission of IOP Publishing.) (b) (b1) Schematic diagram of the processing steps used to fabricate TiO₂ nanofiber mats on Al₂O₃ substrates with interdigitated Pt electrode arrays. (b2) A calcined TiO₂ nanofiber mat on top of the Al₂O₃ substrate and Pt electrode (bright region). (b3) Gas sensor (10 mm × 15 mm) with TiO₂ nanofiber mats after different processing steps. (Reprinted from ref. 95 with permission of American Chemical Society.)

However, devices based on carbon nanotubes or semiconducting nanowires generally suffer from high noise levels and low reproducibility due to the high statistical variations between single nanowire devices.⁹⁵ In this regard, the use of multiple nanowire networks could overcome these problems by averaging out the noise level and hereby also leading to more reproducible systems.

The high suitability of electrospun nanowires for sensitive gas detection was proven in multiple studies, where preliminary reports of electrospun 150 nm diameter MoO₃ fibers led to detection levels of 50 ppm of NO₂ in air.⁹⁶ A great number of studies on electrospun gas sensors have been published to date, and have been reviewed by Ding *et al.*,⁹⁷ leading to a great variety in polymer materials used and types of gases which can be detected. One example of a common system is the use of polyacrylic acid (PAA) which can readily detect ammonia through interaction with the carboxyl groups on PAA. In this regard, the fabrication of 215 nm diameter, succinic acid-treated chitosan/PAA composite fibrous membranes led to an 8-fold increase in sensitivity compared with thin film sensors, reaching a detection threshold as low as 50 ppm.⁹⁸ The high potential of electrospun fibers was also demonstrated

by Yang *et al.*,⁹⁹ who compared SnO₂ nanofibers with multiwalled carbon nanotube-doped SnO₂ fibers for detection of carbon monoxide. Where the pure SnO₂ fibers could not lead to any clear detection of carbon monoxide levels below 500 ppm, the inclusion of the carbon nanotubes boosted the sensitivity to below 50 ppm at room temperature, highlighting the importance of dopants for high sensitivity. It is important to note that upon comparing the performance of such fibers, careful attention must be paid to the fact whether these fibers can work properly in humid atmospheres as humidity has been known to be a major source of interference.¹⁰⁰ By careful selection of the polymer material, the selectivity for a certain type of gas can be improved, however, as shown for ammonia detection by PAA-fibers whose selectivity does not alter up to 45% humidity.⁹⁸

The detection levels of most electrospun fibrous membranes for gas sensing were in the lower ppm range, although several studies have made important breakthroughs in further enhancing the sensitivity. Ding *et al.*¹⁰¹ employed electrospun PAA fibers and used these fibrous membranes to coat QCM electrodes. Compared with cast film coated QCM sensors, the sensitivity towards ammonia was increased nearly 4-fold,

1 leading to clear detection of ammonia at levels as low as
130 ppb and in humid atmosphere (40% humidity), which was
attributed to the high porosity. Importantly, it was shown
that the sensitivity of the sensors related strongly to the
morphology of the electrospun fibers, which could easily be
modified by altering the electrospinning conditions. As an
example, fibers spun in 100% water, 50/50 ethanol/water
mixture and 100% ethanol had diameters of, respectively,
1.1, 6.7 and 2.0 μm and their rigidity increased with higher
ethanol concentration.

Further improvements in sensitivity for NO_2 was achieved
by Kim *et al.*⁹⁵ who produced TiO_2/PVA composite
nanofibers of 200–500 nm diameter which were spun directly
on Pt electrode arrays (Fig. 14b). This led to a nanowire
network composed of multiple nanofiber sheets filled with
single crystal anatase fibrils, one of the three mineral forms
of TiO_2 characterized by sharply developed crystals, which
were readily gas-accessible. The size of the gas-accessible
fibrils, approximately 10 nm thick, was comparable to the
typical width occupied by the gas-modulated space charge
region, which greatly increased the sensitivity of the system.
From these data, a detection limit of below 1 ppb was
estimated, being one of the most sensitive gas detection
systems so far. This study demonstrated the importance of
the size of the gas-accessible regions, which, when approaching
the typical size occupied by gas molecules, can greatly enhance
sensitivity of detection. This finding can easily be applied to
other fiber detection systems as well; where advances might
still be possible by increasing the adhesion of the fibers onto
the electrodes (for instance by coating the latter with a high
conducting polyelectrolyte, as discussed in Section 2.5).

2.5.5 Ethanol-responsive electrospun fibers. A strong focus
has been put on the detection of trace amounts of (gaseous)
ethanol, for instance to improve breathalyzer tests.¹⁰² In this
regard, ZnO nanowires have long been used for ethanol
detection as they exhibit a high sensitivity at elevated
temperatures.¹⁰³ In ambient air, oxygen molecules are caught
on the fibers, forming oxygen ions which significantly increases
the resistance of the fibers. Exposure to ethanol has a reducing
effect, which releases electrons from the conducting band of
oxygen ions and rapidly decreases the fibers resistance. When
ZnO nanowires are prepared using a classical self-catalyzed
vapor–liquid–solid method, the sensitivity for ethanol at
lower temperatures rapidly declines and the response and
recovery times are generally low (10 and 55 s, respectively).
To overcome these problems, Wu *et al.*¹⁰³ prepared electro-
spun ZnO nanofibers which were found to exhibit an excellent
sensitivity, owing to the high surface area and porosity of
the electrospun fibers which significantly enlarges the total
fiber-ethanol interface.

To achieve efficient and high sensitive detection of ethanol,
 SnO_2 has also been widely explored as a good sensing material
and efforts were made to use SnO_2 for electrospinning.¹⁰⁴ In
microsensing devices, SnO_2 has however been rarely used, due
to the relative inefficiency to spin the fibers onto the small
sensing area of a microsensor. Zhang *et al.*¹⁰⁵ devised a
strategy to obtain SnO_2 nanofibers coated onto a micro
heating plate by directly electrospinning $\text{PVA}/\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$

composites on the top of the microsensor. With PVA concen-
trations ranging between 5 and 8 wt%, 100 nm fibers could be
achieved. By adjusting the electrode-to-collector distance, the
deposition areas of the electrospun fibers could be controlled,
finally matching the sensing area of the micro heating plate
(2 mm^2). The SnO_2 nanofiber-coated sensor displayed a nice
linear response–concentration relationship in the 1–5000 ppm
range with a detection limit of below 10 ppb, highlighting the
great sensitivity of the fabricated microsensors. Further
increases in sensitivity and response rates may be achieved
by the use of dopants, as was shown by Liu *et al.*,¹⁰⁶ who
compared pure and Pd-doped In_2O_3 electrospun fibers of
120 nm diameter and found a near 4-fold increase in sensitivity
for Pd-doped fibers. Nickel nanoparticle-doped carbon fiber
paste electrospun fibers have also been used for ethanol
detection in liquor samples, indicating a high linear response
(up to 87.5 mM) and a sensitive detection limit as low as
0.25 mM.¹⁰⁷ The combination of the different studies, using
doped fibers deposited onto a well-controlled area of a micro-
sensor device, may lead to fast and highly sensitive detection
devices.

2.5.6 Reduction-responsive electrospun fibers. The use of
fibers in tissue engineering has gained a lot of popularity, due
to the high porosity, adequate mechanical strength and high
spatial interconnectivity within a fibrous network, which
greatly resembles the natural extracellular matrix, which
supports cell growth in the body.^{108–110} Electrospinning
water-soluble polymers requires crosslinking of the obtained
fibers to generate a stable matrix under physiological conditions.
This crosslinking can, however, impede (enzymatic) degradation
of the fibers or even induce cytotoxic effects or inflammation in
tissues due to lowering of the pH upon *e.g.* hydrolysis
of crosslinks.¹¹¹ To overcome these issues, Wang *et al.*¹¹²
reported on biocompatible and highly branched fibers derived
from poly(2-hydroxyethyl methacrylate) crosslinked by
disulfide bridges. The latter groups allow us to tightly control
the degree of crosslinking by adjusting the concentration of
non-toxic reductants such as glutathione or cysteine. A good
control over the amount of crosslinks is important *e.g.* to
optimize cell growth and to allow a controllable degradation
of the fibers after transplantation. Yoshida *et al.*¹¹³ employed
the latter findings to generate biocompatible and biodegradable
poly(γ -glutamic acid) (γ -PGA) electrospun fiber scaffolds with
disulfide crosslinks. These fibers could be nearly completely
decomposed within 1 h after exposure to 5 mM L-cysteine.
Furthermore, the fibers were well-suited for the culture of
L929 murine fibroblasts, as displayed by the rapid cell cycle
progression. Clearly, such fibers may offer a wide range of
tissue engineering applications as they allow a well-controlled
degree of crosslinking and can be efficiently broken down in
the body without causing inflammation or cytotoxicity which
is typically associated with persisting fiber scaffolds or
uncontrolled hydrolysis.

2.6 Electric field-responsive electrospun fibers

As indicated in Section 1.3, electric current can readily
affect the diameter and morphology of electrospun fibers by
influencing the polymer flow rate. During the electrospinning

1 process, the electric field is therefore fundamental to achieve
nicely electrospun fibers, as for higher electric currents, bead
formation is likely to occur.¹¹⁴ Electric fields can also be used
in more advanced setups, for instance by using dual fields
5 where the secondary electric field is perpendicular to the
primary field. Using this approach, the orientation of the
fibers on the collector can be well controlled, resulting in
nicely aligned fibers.¹¹⁵ Alternatively, electric fields can
also influence the swelling behavior of electrospun fibrous
10 membranes. Li and Hsieh¹¹⁶ prepared electrospun poly(acrylic
acid) and poly(vinyl alcohol) (17–83%) fibers and investigated
the swelling behavior of the fibers when exposed to aqueous
solvents. At different pH values (especially for a pH
value between 4 and 7), pronounced swelling of the fibrous
15 membranes was observed. When exposed to an electric field,
the swelling ratios further increased (from nearly 11 to 20 at
pH 4). This increased swelling was also accompanied by
increased width and thickness of the membranes. These
data show that the pH-dependent swelling behavior of the
20 electrospun membranes can be further augmented by the
application of an electric field.

2.7 Multi stimuli-responsive electrospun fiber systems

25 Generally speaking, dual stimuli-responsive polymers could
further enlarge the already wide area of applications suggested
for polymers which can be triggered by only one single
stimulus. For instance, in drug delivery triggered release of
the active compound by multiple stimuli might further
30 improve the specificity of drug release. Chen and Hsieh¹¹⁷
studied electrospun pNIPA/PVA copolymer fibers which are
both pH and temperature sensitive. At room temperature and
at a pH below 4, the fibers showed nearly no swelling, whereas
strong swelling was observed above pH 4. In contrast, at
35 elevated temperatures (70 °C) the swelling degree of the fibers
reduced from 15 to 2.6-fold. Chunder *et al.*¹¹⁸ fabricated
PAA/PAH electrospun fibers and incorporated methylene
blue (MB), a low molecular weight cationic molecule, as a
model drug to evaluate release from the fibers. As PAA and
40 PAH are both weak polyelectrolytes, the release of MB could
be triggered by adjusting the pH of the medium. At pH 7 or
higher no release of MB was observed as the cationic MB
molecules bind to the anionic carboxylate groups on PAA.
Release occurred at pH 6 and lower as more carboxylate
45 groups on PAA become neutralized. Depositing a pNIPA
coating on such fibers, which hereby creates polyelectrolyte
multilayer fibers, allowed MB to be released in a temperature-
dependent manner (nearly 10-fold faster at 40 °C than at
25 °C). All these data taken together, it is evident that the
50 combination of the unique properties of polyelectrolyte
electrospun fibers and polyelectrolyte multilayer films will
undoubtedly lead to versatile controlled release systems.

Ionic strength and pH sensitive PAA/polymaleic acid
(PMA) electrospun nanofibrous membranes were designed
55 by Liu *et al.*¹¹⁹ Fibers of about 120 nm diameter were
produced which were crosslinked by diethylene glycol
(DEG). Compared with acrylic acid (pK_a near 4), which is
present in most pH-responsive hydrogels, maleic acid has two
protons with different pK_a values, respectively, 1.5 and 6.5.

The upper pK_a value lies within the physiological pH range
6.8–7.4 which may make PAA/PMA fibers of interest for
biomedical applications. The swelling behavior of PAA/
PMA fibers seemed sensitive to both ionic strength and pH.
Upon increasing the pH, the swelling of the fibers showed a
5 dual transition between pH 2.5 and 4.6 the swelling ratio
increased 3- to 4-fold, then leveled off up to pH 8.5 after which
a second significant increase was noted from pH 8.5 to 11.

3. Emerging biomedical applications of electrospun fibers and webs

As electrospinning has gained a lot of popularity during the
last decade, the number of potential *biomedical* applications is
also vastly increasing. Classically, electrospun fibers were
15 primarily studied for (a) tissue engineering¹²⁰ due to the high
morphological similarities with the natural ECM, (b) wound
dressing, where phase III clinical trials were encouraging, and
(c) drug delivery.^{3,121,122} The further development of methods
for electrospinning and the vast amount of data generated in
20 the last decade have given rise to novel potential applications.
Some of them, *i.e.* encapsulation of cells and protection of
drugs against counterfeiting, are discussed below.

3.1 Co-encapsulation of living biological samples

As mentioned above, biological applications of electrospun
fibers have been limited to the development of biocompatible
nanofibers for tissue engineering or drug release,¹²³ or to
the immobilization of cells on nanofiber scaffolds.¹²⁴ The
30 inauguration of core-shell fibers, prepared by co-electrospinning
of two polymer solutions without direct mixing, offers a
number of advantages as the shell may protect the core
material during the electrospinning process.¹²¹ Jiang *et al.*¹²⁵
demonstrated the effective protection during electrospinning
35 of BSA (in a dextran core) by a poly(ϵ -caprolactone) shell;
BSA was kept intact as was verified upon examining the
protein after its release in the surrounding environment. Next
to proteins, even living cells such as bacteria and mammalian
cells were safely encapsulated within electrospun fibers. Liu
40 *et al.*¹²⁶ reported on the fabrication of polyethylene oxide₉₉-
polypropylene oxide₆₇-polyethylene oxide₉₉ triblock polymer
fibers by electrospinning and the encapsulation of microbes
from three industrially relevant genera (Fig. 15). The entrapped
microbes were viable for several months, with no change in
45 their metabolic activity. This opens the door to the generation
of synthetic biofilms and the use of novel bio-hybrid materials.
Using poly(dimethylsiloxane) (PDMS) as shell material,
mammalian cells were also found to be efficiently encapsulated
together with their culture media without any significant
50 cellular damage.¹²⁷ All these data indicate the potential of
electrospinning for applications which require the formation
of active biological scaffolds.

3.2 Protecting drugs from counterfeiting by electrospun fibers

Drug counterfeiting is an ever increasing problem, recognized
by all official health institutes and pharmaceutical
organizations.¹²⁸ To date, most protective measures relate to
the application of tags or marks (barcodes, fluorescent marks)

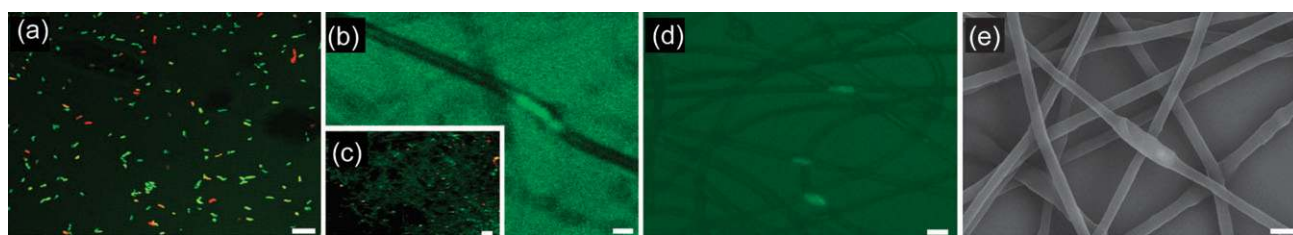


Fig. 15 Confocal images of (a) *P. fluorescens* before electrospinning, (b and c) inside dry electrospun FDMA/PEO-blend fibers and (d) *Z. mobilis* in dry electrospun FDMA/PEO-blend fibers. (e) SEM image of *P. fluorescens* in electrospun fibers. Scale bars, 10 μm in (a), 1 μm in (b), 20 μm in (c), 2 μm in (d) and 1 μm in (e). (Reprinted from ref. 126 with permission of National Academy of Sciences USA.)

on the drug packaging. As many drugs are, however, repackaged by wholesalers to unit-of-use containers, the protective mark on the packaging is lost and counterfeit drugs can enter the legitimate drug supply chain. In order to overcome these problems, “in-drug labelling” itself may provide the most effective protection mechanism.

Recently we proposed micron-sized electrospun fibers fabricated from pharmaceutical polymers (like cellulose acetophthalate (CAP) and PLGA; which are commonly used as excipients in drug formulations for oral use)¹²⁸ for

the in-product labelling of tablets.¹²⁹ By means of electrospinning, fluorescently dyed fibers were obtained which were aligned and cut into micrometre sized pieces using an appropriate scanning UV laser (Fig. 16). Barcodes were written in the fibers through spatial selective photobleaching.¹²⁸ As Fig. 16 explains, the codes in the fibers applied at the tablet’s surface could be easily decoded using a basic fluorescence microscopy setup. This simple and rather inexpensive strategy may initiate the highly desired solution to in-product labelling of pharmaceuticals and may have far-stretched consequences, especially in developing

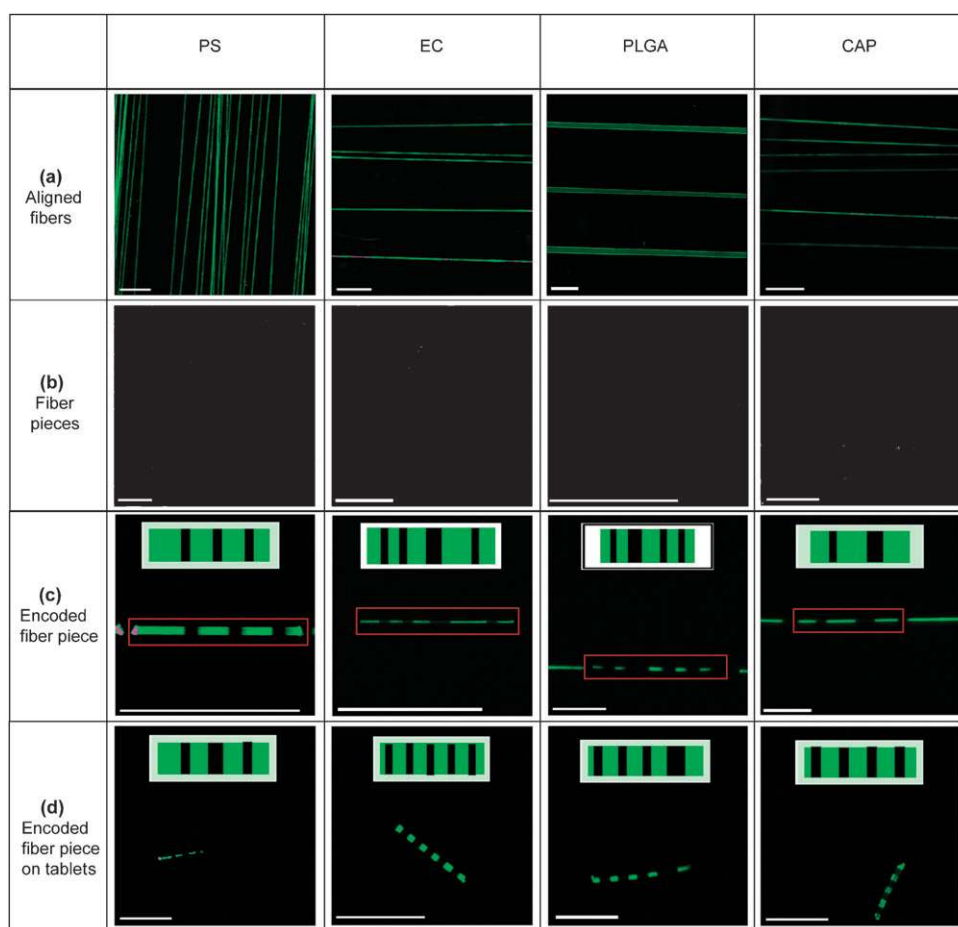


Fig. 16 Fluorescence images of aligned fibers (a) prepared from polystyrene (PS), ethylcellulose (EC), cellulose-acetate-phthalate (CAP) or poly(lactic-co-glycolic acid) (PLGA) and (b, c) fiber pieces loaded with coumarin-6. Panel (d) shows images obtained from fibers at the surface of tablets using a simple fluorescence microscope. The inserts in (c) and (d) show the barcodes which were written in the fiber pieces, the red rectangles indicate one encoded fiber piece. Scale bar is 100 μm . (Reprinted from ref. 128 Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

1 countries where many people suffer from counterfeit drugs of
inferior quality.

4. Conclusions and outlook

Electrospun nanofibers and membranes offer many advantages for a wide range of applications in a variety of fields, including biomedicine, chemical sensing and biotechnology. The biggest advantage of electrospun fibers over other types of polymeric fibers or polymeric nanoparticles is their high surface over volume ratio and very high and tunable porosity which generate a large and easily accessible surface. Especially for stimuli-responsive fibers this is of considerable interest as these features greatly enhance their sensitivity of detection and response rate to external stimuli. Several intrinsic features of electrospun fibers, such as their ability to self-support, tunable mechanical properties and degradability and close resemblance to natural extracellular matrix fibers, further boost the potential applications of these fibers for biomedical applications. Electrospinning is also a highly versatile and facile method as this single technique can produce a great variety in types of fibers with various surface functions. This is in great contrast to the wide variety in preparation methods needed to synthesize and functionalize e.g. nanoparticles.

In the field of drug delivery, targeted and controlled drug release by nanoparticles is a hot research area in which there is still a lot of room for improvement.¹³⁰ Targeting nanoscopic particles after intravenous injection to the desired location in the body while avoiding uptake by liver, kidney and lung remains indeed very challenging. Furthermore, the internalization of nanoparticles by target cells requires a high level of uptake and thus many interactions between the cells and the particles, which can induce cytotoxic effects.^{131,132} Lastly, although a lot of effort has been put in optimizing nanoparticle systems which can escape the endosomal pathway, this is currently not possible with a high efficiency and therefore presents a great limitation for nanoparticle-mediated drug delivery.¹³³ Clearly, as electrospun fibers are not suited for intravenous injection they will not be able to compete with nanoparticles as advanced *injectable* drug carriers. Though, one should realize that as (mats of) electrospun fibers can be easily implanted in the body they may become interesting drug delivery devices in treatments where surgery is already indicated.¹³⁴ Such implanted drug loaded webs are also expected to remain at the desired location (*i.e.* will not drain away, which mostly occurs with drug carrying nanoparticles) being important for the treatment.

Another interesting application of electrospun fibers which has recently been put forward is their use against infectious diseases. Bacterial-derived diseases could be inhibited by encapsulating antibiotics or silver nanoparticles in electrospun fibers, which exert a potent antimicrobial activity.¹³⁵ Furthermore, owing to the intrinsic features of electrospun fibers, fibrous membranes can form effective size exclusion membranes for particulate removal (95–100% rejection) from air or aqueous solutions.¹³⁶ Making use of ligand-decorated electrospun fibers (affinity membranes), protein, toxin and even viral particle removal would become possible.¹³⁶ In this regard, electrospun fibers have been put forward as potent

inhibitors of human immunodeficiency virus (HIV) infection by fabricating an adsorption film, which is a woman condom shaped film which can prevent HIV transmission by adsorption and filtering. Polymer electrospun fiber webs are highly flexible, allowing to fully cover the vaginal mucous membrane, which is needed to produce a female condom shaped film. Nanoparticles cannot support themselves without an extra matrix to form such a film and therefore seem less suited for such applications.

Owing to all these features and the vast array of potential applications, it is expected that electrospun fibers in general and stimuli-responsive fibers in particular will become increasingly important biomedical tools which may introduce a new era of scientific advances to serve mankind.

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