TOPICAL REVIEW

Multifunctional one-dimensional polymeric nanostructures for drug delivery and biosensor applications

To cite this article: Sezin Sayin *et al* 2019 *Nanotechnology* **30** 412001

IOP Publishing Nanotechnology
Nanotechnology 30 (2019) 412001 (17pp) https://doi.org/10.1088/1361-6528/ab2e2c

Topical Review

Multifunctional one-dimensional polymeric nanostructures for drug delivery and biosensor applications

Sezin Sayin[1], Ece Ozdemir[1], Egemen Acar[1] and Gozde Ozaydin Ince[1,2,3]

[1] Materials Science and Nano Engineering, Faculty of Engineering and Natural Sciences, Sabanci University, 34956 Istanbul, Turkey
[2] Sabanci University Nanotechnology Research and Application Center (SUNUM), 34956 Istanbul, Turkey
[3] Center of Excellence for Functional Surfaces and Interfaces (EFSUN), Sabanci University, 34956 Istanbul, Turkey

E-mail: gozdeince@sabanciuniv.edu

Received 1 March 2019, revised 25 April 2019
Accepted for publication 1 July 2019
Published 26 July 2019

Abstract

Advances in nanotechnology in the last decades have paved the way for significant achievements in diagnosis and treatment of various diseases. Different types of functional nanostructures have been explored and utilized as tools for addressing the challenges in detection or treatment of diseases. In particular, one-dimensional nanostructures hold great promise in theranostic applications due to their increased surface area-to-volume ratios, which allow better targeting, increased loading capacity and improved sensitivity to biomolecules. Stable polymeric nanostructures that are stimuli-responsive, biocompatible and biodegradable are especially preferred for bioapplications. In this review, different synthesis techniques of polymeric one-dimensional nanostructures are explored and functionalization methods of these nanostructures for specific applications are explained. Biosensing and drug delibiovery applications of these nanostructures are presented in detail.

Keywords: one-dimensional polymer nanostructures, drug delivery, biosensors, functionalization of nanostructures, synthesis of one-dimensional polymer nanostructures

(Some figures may appear in colour only in the online journal)

1. Introduction

The application areas of nanostructures range widely from medicine to military applications. Nanostructures with their controlled size and tunable responses to stimuli attracted much attention in the biotechnology fields such as tissue engineering, drug delivery systems and biomedical applications [1–4].

Polymers are generally the choice of materials for biomedical applications due to their biodegradable and biocompatible nature and their chemical and physical properties that can be tailored for specific applications [5, 6]. Smart polymers such as pH sensitive, temperature-sensitive, phase-sensitive, light-sensitive, biomolecule-sensitive polymers can be used for controlled and triggered drug delivery systems [7–9]. Polymers, through interactions with biomolecules, also bring long-term stability and improve reliability of the system [10].

One-dimensional polymeric nanostructures have advantages over their zero-dimensional or higher dimensional counterparts due to their high surface area-to-volume ratios, thermal stability and mechanical properties [11, 12]. On the other hand, 1D conducting polymer nanostructures have additional advantages due to their high conductivity, high carrier mobility and exceptional electrochemical activity [13, 14]. 1D nanostructures have also been integrated as the

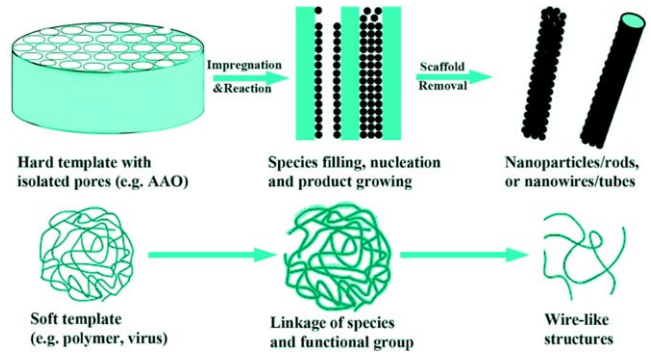

Figure 1. Schematic illustration of hard and soft templated synthesis methods. Reprinted with permission from [21] Copyright 2008 American Chemical Society.

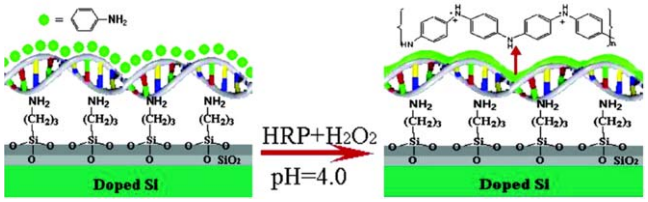

Figure 2. DNA chains immobilized on Si surface used as a template for aligning the aniline monomers. Formation of PANI nanowires aligned on the DNA chains. Reprinted with permission from [27] Copyright 2004 American Chemical Society.

sensing or transducing elements of a sensor, resulting in higher sensitivity due to their high surface area-to-volume ratios [15].

Nanostructures such as nanotubes, nanofibers and nanowires can be used as drug delivery vehicles, due to their high drug loading efficiency, encapsulation effectiveness, compatibility with physicochemical agents and ability to adjust drug release [16–20]. Nanotube-based controlled drug delivery has further advantages. They entrap the drug molecules and protect them against denaturation or degradation during the delivery process. Since nanotubes have large inner volumes, they also enable the loading of more than one therapeutic agent with the possibility of simultaneously using targeting molecules, contrast agents, drugs or reporter molecules.

In this review, polymeric 1D nanostructures, their most commonly used fabrication techniques and methods to impart these nanostructures further functionalities are detailed. Compared to other reviews on polymeric nanostructures, which either focus on a specific fabrication technique or nanostructure, or broadly cover all types of nanostructures, this review focuses specifically on polymeric 1D nanostructures and presents an extended review on the fabrication methods. In the last part of this review, among many different bioapplications of these polymeric nanostructures, biosensing and drug delivery applications are reviewed and the effects of the nanostructure properties on their performance are discussed.

2. Synthesis

One-dimensional polymeric nanomaterials associated with biomedical applications are fabricated by using solution or vapor phase synthesis techniques, depending on the application.

2.1. Solution-based synthesis methods

2.1.1. Template assisted synthesis methods. Template assisted solution-based synthesis methods are classified as soft and hard templated methods. Their schematic illustration is given in figure 1 [21].

Among wide range of soft templates anisotropic cylindrical micelles, colloidal particles, structure-directing molecules, liquid crystals or thiolated cyclodextrins and polyacids are few of the commonly used ones [5, 22–24]. These templates can be used to obtain various 1D structures, i.e. conductive or functional polymeric nanofibers, nanotubes or nanowires [25]. Soft-templates are advantageous because they can be used in a basic self-assembly procedure with no need for additional fabrication steps. However, uniform shape and diameter control throughout polymeric 1D nanostructures is hard to obtain with soft templates [26].

DNA is another commonly used template as it has very good recognition capability and acts as a smart glue. In Ma *et al* [27], double bonded DNA stretched and immobilized on a Si surface is incubated in aniline solution. As a result, aniline monomers were aligned and organized along DNA chains to form polyaniline nanowires as shown in figure 2 [27]. In another study, Nickels *et al* synthesized also DNA-templated polyaniline nanowires by three different methods; pH mediated oxidative polymerization, enzymatic oxidation and photo-oxidation [28]. Oxidative polymerization with ammonium persulfate was found to be the best suitable technique for DNA-templated polyaniline nanowire synthesis. In this method, oxidoreductase horseradish peroxidase (HRP) catalyzed the reduction of hydrogen peroxide and resulted in the oxidative polymerization of aniline [28]. Watson *et al* [29] formed poly-2,5-bis(2-thienyl)pyrrole (p(TPT)) nanowires by oxidation of TPT in DNA-involving solvent and $FeCl_3$. They also investigated the conductive supramolecular nanowire formation mechanism by multiscale modeling and atomic force microscopy (AFM). Maximization of interactions between DNA-conducting polymer (CP) and CP–CP, and surface energy reduction resulted in smooth regular nanowire structure.

Hard-templates, on the other hand, provide spatial control, as in coaxial nanowires, and tuning of the chemical composition [5]. However, the functionalization of nanofiber walls, and the need for post-synthesis processes such as template etching can be problematic in synthesis using templates. Among hard-templates, alumina silicate, zeolite channels, track-etched polycarbonate, anodic aluminum oxide (AAO) and particle track-etched membranes are commonly used ones [11, 30]. Steps to synthesize polymeric 1D nanostructures with hard-templates include filling the pores of the template with the precursors, followed by polymerization in the pores, and template removal as the final step [31]. Filling of the template pores can be achieved by liquid injection, applying negative pressure, and immersing the

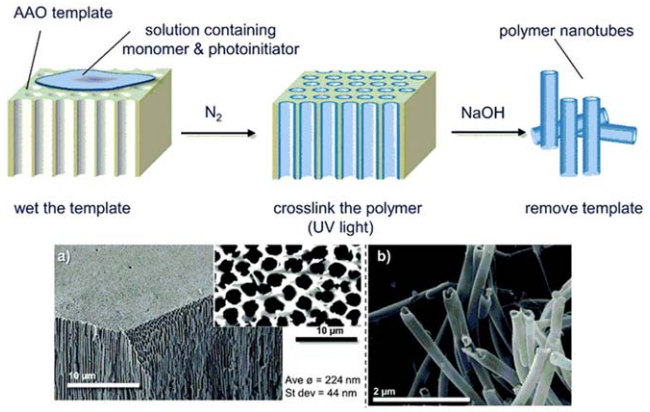

Figure 3. Nanotube synthesis using AAO templates by photopolymerization (above), SEM images of (a) AAO template and (b) PEG nanotubes. Reproduced from [33] with permission of The Royal Society of Chemistry. CC-BY 3.0.

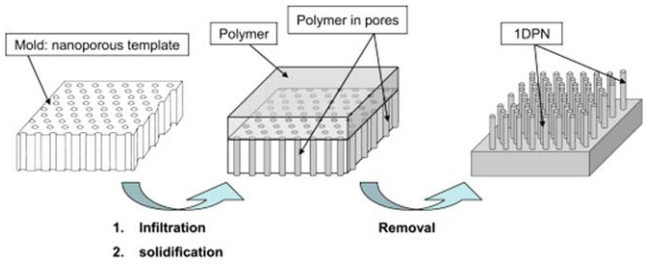

Figure 4. Nanomolding process scheme. PE film is first infiltrated and solidified on AAO templates. Removing the template releases the 1D PE nanowire arrays. Reprinted from [42] Copyright 2012 with permission from Elsevier. CC BY-NC-ND 3.0.

template in a precursor solution. During polymerization, oxidizing or electrochemical polymerization can be used to synthesize conducting polymeric nanofibers [11].

Besides nanofibers, nanotubes can also be synthesized by templates and have advantages over nanofibers due to their large inner volumes and large surface area/volume ratios. Separate control of the length and diameters of the nanotubes, as well as their alignment are crucial for certain applications such as neural interface and drug delivery [26]. In synthesis methods via templates, nanotubes are formed by depositing the polymer in the cylindrical pores of these templates. The size of the pores determine the outer diameter of nanotubes, whereas the inner diameter of polymeric nanotubes is specified by the polymerization time [4, 26, 32]. Similar to nanofibers, control of the nanotube structure and composition is achieved by varying the parameters such as monomer concentration, or reaction time in the hard template assisted method [33]. Newland *et al* [33] demonstrated poly(ethylene glycol) (PEG) nanotube synthesis by photopolymerization with AAO templates as shown in figure 3. In the synthesis process, the precursor solution containing the monomer and a photoinitiator was filled into the pores of the template, followed by crosslinking via UV light exposure. Removing the template released the polymer nanotubes.

Polyethylene glycol (PEG) [34], poly(glycidyl methacrylate) (PGMA) [35], poly(methyl methacrylate) (PMMA) [36], polystyrene [37], polypyrrole (PPy) [38], poly(3,4-ethylenedioxythiophene) (PEDOT) [39], and PANI [40, 41] nanotubes were synthesized by specific templates.

A different template-based technique is the nanomolding process, which utilizes a hard, porous template as a mold. In this technique, the polymer solution is infiltrated into the template pores, where it solidifies, followed by the removal of the template (figure 4) [42]. Nanomolding differs from the previous techniques as it does not involve polymerization reactions within the pores.

Infiltration is the key step of nanomolding enabling the control of the shape and final morphology. The infiltration step can be spontaneous or by applying an external force such as pressure or field gradients [42]. Cao *et al* [43] synthesized polyethylene (PE) nanowire arrays having high thermal conductivity and superhydrophobicity by nanomolding process. They used porous anodic alumina templates and placed PE film on to this template. Infiltration was achieved in an oven at 160 °C with vibration from piezoelectric transducer at frequency of 10 kHz to melt PE film. After cooling the sample, template was removed by NaOH solution.

2.1.2. Template-free synthesis methods. In template-free methods, the polymer nanostructures form in certain directions regulated by molecular interactions in the absence of templates [26]. Template-free approach eliminates the final template removal step, simplifying the process. However, poor control on the morphology and alignment of the nanostructures are significant short-comings of these methods [26].

The template-free methods are mainly based on self-assembly and interfacial polymerization [44, 45]. Polyaniline (PANI) nanofibers are one of the most commonly synthesized nanostructures via template-free, chemical /electrochemical oxidation polymerization [46–51].

Huang *et al* [44] reported PANI nanofiber fabrication by chemical oxidative interfacial polymerization in acidic environment. In this technique, an immiscible aqueous/organic two-phase system was used, where the aniline was in the organic phase and the oxidant was in the aqueous acid. At the interface of these two layers, where the polymerization occurs, the presence of the hydrogen bonding, π–π interaction, electrostatic forces and van der Waals forces resulted in nanofiber formation and the morphology of nanofibers was dependent on the acidic content of the solution [26].

Additionally, conducting polymeric nanotubes can be synthesized by pH polymerization. In the chemical oxidative template-free method, different inorganic acids are used for conducting nanotube synthesis. For example, ammonium persulfate has been used as oxidant and decrease in pH during oxidation yields template-free PANI nanotube synthesis [52]. Feng *et al* [53] synthesized PPy nanofibers via self-assembly with Acid Red B dopant and $FeCl_3$ oxidant. Furthermore, Fan *et al* [54] fabricated polydopamine nanofibers with folic acid by ordered stacking of oligomers in the structure.

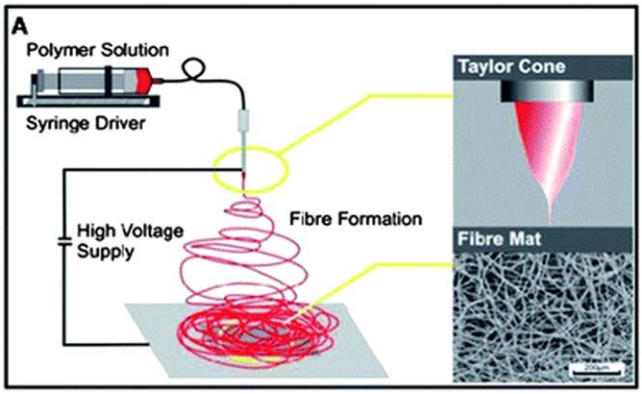

Figure 5. Electrospinning schematic showing grounded spinneret, high voltage power supply and fiber formation. Reproduced from [3] with permission of The Royal Society of Chemistry.

2.1.3. Electrospinning. Electrospinning is another versatile technique to synthesize polymeric nanofibers. As shown in figure 5, the principle is based on a grounded spinneret connected to high voltage power supply [3]. Electrostatic repulsion occurs by the application of high voltage to the spinneret tip. Polymer solution is transferred to spinneret via syringe pump. Surface tension causes pendant droplets at first and with enough voltage taylor cone shape is obtained, resulting in the jet formation directed towards the collector. As the solvent in the solution evaporates on the collector, and polymer nanofibers are obtained on the collectors. These collectors can be copper, aluminum plates or rotating drums.

In electrospinning, polymers that can be used for fiber synthesis are limited. The disadvantage of electrospinning is that non-conducting polymers or additives such as PEO should be used in the conductive polymer fiber formation. These additives decrease the conductivity but results in fine fibers [26]. On the other hand, with respect to other approaches, electrospinning is very useful in mass-production for continuous long nanofibers. Additionally, porosity, surface area, fiber diameter, thickness and brittleness can be adjusted for desired product shape [17, 26, 55–57]. Mortar grinding, ultrasonication, razor blade cutting, and cryogenic cutting are methods forming short nanofibers [58].

Morphology of nanofibers produced by electrospinning depends on the type of the polymer and the solution properties. Polymer properties that affect the fiber morphologies are mainly molecular weight distribution, solubility, and glass-transition temperature. Among solution properties, viscosity, solution concentration, surface tension and conductivity are significant factors that affect the fiber formation. Some other parameters as substrate type, polymer feed rate, electrode geometries, humidity and field strength are also effective [56].

For core–shell structures, coaxial electrospinning is utilized [17]. In core–shell nanofibers, external layer, shell, usually consists of active agents specified for functionality such as immobilized enzymes, whereas inner core layer provides mechanical support or consists of the cargo molecules in delivery applications [59]. Specifically, in biological applications, biomolecules are embedded in the nanofibers as the inner core. Two different solutions in the coaxial nanofiber fabrication process prevents the interaction between aqueous based organic molecules and the solvents in the polymer solution. The fiber diameter is determined by the solution concentration of the shell [17].

Polyvinylpyrrolidone (PVP) [60], polycaprolactone (PCL) [57, 61–63], polyurethane (PU) [61], polylactide (PLA) [57, 64], poly(DL,Lactide-co-glycolide) [65], polyvinyl alcohol (PVA) [57], polyvinylcaprolactam [66], chitosan [67], polyaniline (PANI) [68], polyacrylonitrile (PAN) [68] are main polymers fabricated by electrospinning that are used in biomedical applications.

2.2. Vapor-phase synthesis methods

Traditionally vapor phase synthesis method of chemical vapor deposition (CVD) has been used for fabrication of inorganic nanostructures. However, in the last couple of decades, modified CVD techniques have been used to fabricate organic 1D nanostructures [69].

Functional, responsive, biocompatible, or electrically conductive polymers are fabricated by initiated chemical vapor deposition (iCVD) or oxidative chemical vapor deposition (oCVD). iCVD uses the advantages of CVD method to coat surfaces with polymers conformally, without the use of any solvents and enabling tuning of the film properties. Reaction of initiating radicals with precursor monomers through free radical mechanism is the main principle of the iCVD polymerization [69–71] (figure 6). The initiator and monomer precursor molecules, which are in the vapor phase, are introduced into the polymerization chamber where the radical molecules are formed via thermal of light-activated decomposition of the initiator. Conformality control is especially crucial for the synthesis of 1D nanostructures within the pores of sacrificial templates (figure 7), and delivery of the precursors to the surface in the vapor phase provides homogeneous distribution of precursor molecules on the surface [70–72].

Systematic studies on the conformality of the coatings on high aspect ratio surfaces show that the surface monomer concentration and the monomer reactivity are the main factors that affect conformality [73]. The degree of conformality, therefore, can be controlled by tuning the deposition parameters. For the synthesis of polymeric nanotubes via iCVD, sacrificial membranes with track etch pores are used. Deposition of polymer on the pore walls, followed by template etching reveals the nanotubes. Ability to control surface concentrations of the precursors separately, enables to tune the chemical composition and crosslinking density of the nanotubes [74].

The low process temperatures and operating pressures protect the functional groups of the monomer precursors, enabling synthesis of functional and stimuli responsive nanotubes [74]. Through thickness control, multilayer 1D nanostructures can also be fabricated by subsequent coating of pores with different polymers. Ozaydin-Ince *et al* [72] fabricated coaxial shape-memory polymer p(TBA-co-DEGDVE)/p(HEMA-co-EGDA) nanotubes via templated iCVD method using AAO sacrificial templates. The coaxial

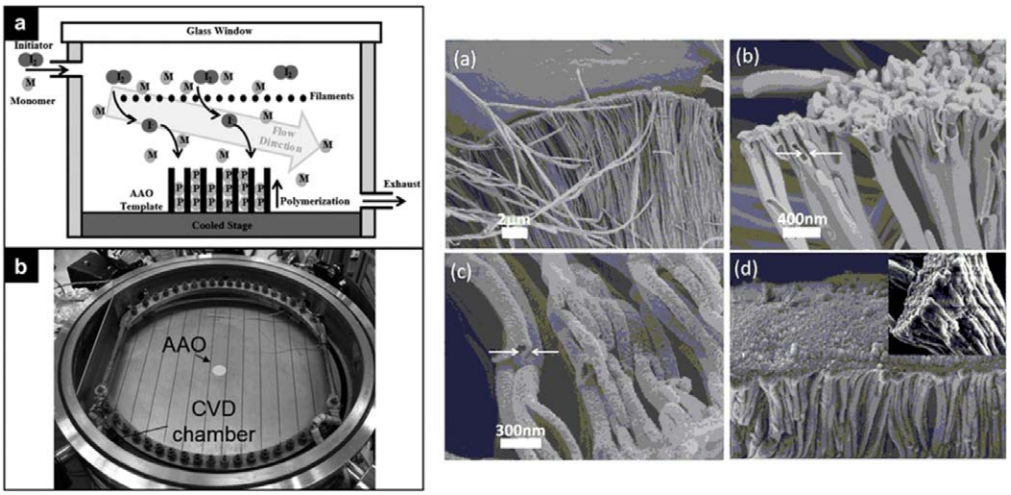

Figure 6. iCVD System used for 1D nanostructure synthesis. (Left) Reproduced from [74] with permission of The Royal Society of Chemistry. SEM images of the stimuli responsive polymeric nanotubes synthesized by iCVD. (Right) Reproduced from [71] with permission of The Royal Society of Chemistry.

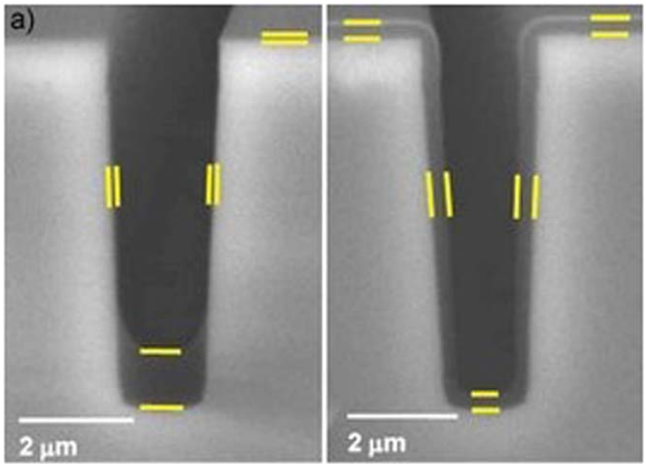

Figure 7. Comparison of the poor step coverage in spin-coated micro-trenches (left), and conformal coverage of the micro-trenches by a thin polymer film via iCVD (right). [70] John Wiley & Sons. Copyright © 2010 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

nanotubes were synthesized by the subsequent coating of the template inner walls with different functional polymers. The shape memory response of the outer polymer layer was activated by the swelling of the inner hydrogel layer. The nanotubes were then used for the burst release of the cargo molecules. Armagan *et al* [71] reported synthesis of stimuli responsive coaxial pNIPAAm/pHEMA/pMAA nanotubes via iCVD (figure 6). Each layer was a different functional polymer, responsive to different stimuli, which enabled the control of the release kinetics. The response of each layer could be controlled separately by tuning the chemical composition of the polymer layers.

Another polymer coating method that is based on CVD is the oxidative CVD method, which is used to deposit conducting polymers. In this method, oxidant precursors replace the initiator molecules and the polymerization reaction occurs between the oxidant and monomer molecules forming the basis of step growth polymerization. Electrical conductivity of the nanostructures synthesized by oCVD comes from the doping process and charges in the conjugated backbone of the polymer [69].

Gap Im *et al* [75] deposited conformal poly(3,4-ethylenedioxythiophene) films via oCVD using $CuCl_2$ as the oxidant. Substrate temperature was varied between 20 and 100 °C to achieve conformal coatings on high aspect ratio structures. Balkan *et al* [76] combined iCVD and oCVD techniques to produce coaxial polymeric nanotubes for sensor applications. The conductive outer layer was polyaniline deposited by oCVD and the hydrogel inner layer was p(HEMA) deposited by iCVD. Thickness and roughness control of each layer was achieved by tuning the parameters such as annealing temperature.

Vapor deposition polymerization (VDP) technique is another widely used technique to fabricate polymeric 1D nanostructures. This VDP technique is classified as self-assembling, bottom-up process and it enables ordered nanostructures from organic arrangement of molecules. PANI nanofibers were formed from aniline monomer in the presence of HCl and APS, via interaction between the aniline vapor and acidic APS. Nanofibers emerged during the stirring of aqueous phase. Polymers formed by this technique are thermally stable, soluble, but less conductive [77].

Highly conductive PEDOT nanotubes and nanorods were synthesized also by VDP technique with AAO templates. First, $FeCl_3.6H_2O$ oxidant in THF was introduced on to template, then, EDOT monomer was given to the system in vapor phase and the polymerization occurred within the pores of the template. The nanotube size was controlled by tuning the deposition temperature and duration [78]. Lee *et al* [79] synthesized poly(acrylonitrile) nanotubes by VDP. Acrylonitrile monomer, 2,2-azo-bis-(2,4-dimethylvaleronitrile) initiator and non-reactive heptane vapor were introduced to the chamber. Heptane/monomer ratio was adjusted for controlling the wall thickness [79]. Polypyrrole nanotubes [80], PEDOT nanofibers and nanotubes [81], and poly(p-xylene) nanowires [82] are further example nanostructures formed by VDP technique.

2.3. Lithography

Lithography-based techniques are often employed in the synthesis of one-dimensional polymeric nanostructures, due to the ability to control the position and the size of the polymeric nanowires simultaneously during synthesis. Dip-pen, nanoimprint and soft lithography are examples to the most commonly used lithographic techniques [83].

In lithography, nano-sized lines are patterned on a substrate coated with a protective polymer coating. Removing the polymer coating exposes the patterned substrate, which can be further etched or doped. During photolithography, a light-sensitive polymer coating, i.e. a photoresist, is used to coat the substrate surface. Exposing the polymer to UV light, develops and hardens the polymer coating. As the final step, the polymer is stripped away and the patterned surface is obtained [84]. Type of polymer coating used, the patterning method, process temperature and development time are some of the important parameters that effect the surface patterns formed [85].

Song *et al* [85] fabricated ordered polystyrene nanotube and nanowire arrays by photolithography in porous AAO templates. Patterning of the AAO template was achieved by first spin coating the photoresist on AAO, followed by UV exposure and hard bake processes to ensure crosslinking. Polystyrene solution was then cast on to the patterned AAO templates, resulting in the formation of the nanostructure arrays. The solution concentration affected the nanostructures formed; at lower solution concentrations (6 wt%) nanotubes and at higher concentrations (10 wt%), nanowires were obtained. In addition to the polystyrene nanotube arrays [86], fabrication of highly ordered polyamide nanotube arrays has also been demonstrated by photolithography and solution wetting methods [87]. Werake *et al* [88] reported polyaniline nanofibers synthesized by UV light illumination of the spin coated precursors on the substrate. In the shaded region, bulk polyaniline was observed whereas in the exposed region, nanofibers were obtained. This work showed that polymeric nanofibers can be incorporated into devices via photolithography.

In nanoimprint lithography (NIL), previously synthesized topographical features of a mold can be transferred to a polymeric surface with the assistance of temperature or solvent vapor. This mold is generally hard with a pattern to emboss the resist. NIL is more advantageous than optical lithography because the resolution does not rely on scattering, wave diffraction, resist interference or back-scattering. The fabricated polymeric nanowire arrays are aligned parallel or perpendicular enhancing their performance. For instance, high temperature NIL provides higher degree of crystallinity for nanowires [89]. Muanchan *et al* fabricated polystyrene and polypropylene nanofiber arrays with high aspect ratio by thermal nanoimprinting method [90]. Fabricated nanofiber arrays had 50 nm diameter with aspect ratios of 1000 and 2600. They could control the nanofiber length by tuning the press time, pressure, and press temperature.

In soft lithography, elastomeric blocks with patterned surface structures are used. Elastomers with low glass transition temperatures, which are fluid at room temperature are preferred [91]. PEDOT-PSS nanowires were synthesized with soft lithography by Zhang *et al* [92]. They achieved to pattern metallic conducting polymeric nanowires by liquid printing and micromolding in capillaries. In this study, height and width of nanowires were also controlled for specific applications of optical gratings and electrodes. Jiang *et al* [93] also fabricated PEDOT-PSS nanowires using a hybrid stamp with nanochannels, which were synthesized by NIL. The stamp was first attached to the substrate forming parallel nanochannels, which were then filled with the polymer solution by capillary forces. As the last step, nanowires were detached from the channels and solvent was evaporated. Tang *et al* [94] reported sub-100 nm PEDOT-PSS nanowires fabricated by soft lithography for sensor purposes. They used nanomolding in capillaries (NAMIC) technique involving hybrid soft stamp with nano-features, which allows large area patterning. Synthesizing PEDOT:PSS nanowires with soft lithography and integrating these structures to functional sensor were realized for the first time. Fabricated sensor showed enhanced properties such as fast response, high repeatability and increased sensitivity.

Pisignano *et al* [95] fabricated polymeric nanofibers by soft lithography. They succeeded to make these fibers aligned and easily detachable from the substrate. First, periodic grooves were formed by electron beam lithography followed by reactive ion etching. Elastomeric structures were then placed on polymer film and molded. By penetration and UV-irradiation, separation and rearrangement of aligned structures were realized.

Dip-pen nanolithography (DPN) utilizes an AFM tip instead of a photomask for the nanostructure synthesis. Typically, an AFM cantilever is coated with ink molecules via dip coating or thermal evaporation processes. These molecules are then transferred to the substrate upon contact of the AFM tip with the surface, as a result of capillary motion. Lim *et al* [96] patterned sulfonated polyaniline nanowires on silicon substrates by using electrostatic interaction as the driving force. Width of the polymeric pattern was controlled by the contact time. Maynor *et al* [97] synthesized sub-100 nm conducting PEDOT nanowires on semiconducting and insulating surfaces by DPN method. Applied voltage, humidity and tip translation speed were varied to control the morphology of polymeric nanowires. This technique is site-specific allowing complicated structures to be synthesized at laboratory scale with multiple inks.

3. Functionalization

Functionalization of the one-dimensional nanostructured materials for improved functionality and biocompatibility extends the application areas of these nanostructures and makes them especially attractive for bioapplications [98, 99]. Surface functionalization of nanofibers can be achieved via various methods such as plasma treatment, wet chemical method, surface graft polymerization, and co-electrospinning [100]. Functionalization of the polymeric nanostructures with a broad range of materials such as polymers [101], metals

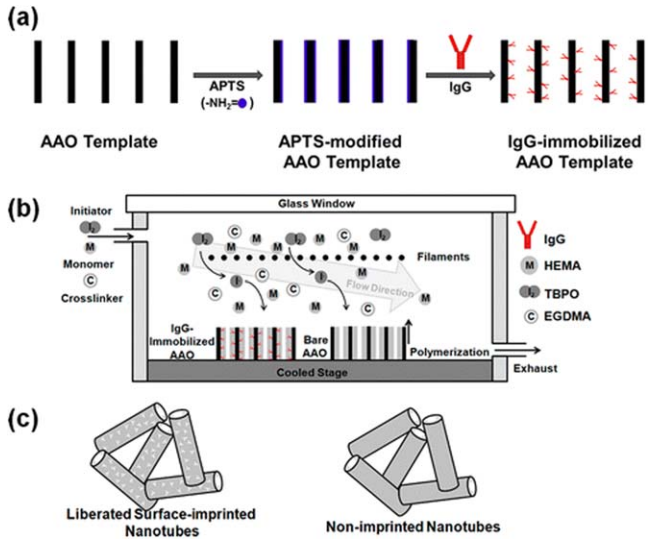

Figure 8. Schematic of fabrication process of surface-imprinted and non-imprinted polymeric nanotubes. Reprinted with permission from [114] Copyright 2013 American Chemical Society.

[102, 103], nanoparticles [104], fluorophores [105], single-walled carbon nanotubes [106] has been reported [107]. In addition, the recognition/binding properties of the one-dimensional nanostructures can be improved by functionalizing them with enzymes, DNA or various biomaterials [107–109].

Matlock-Colangelo *et al* [110] studied the charge dependent separation of bacterial cells by using negatively charged poly (vinyl alcohol) (PVA) nanofibers that were modified with anti- *Escherichia coli* antibodies to capture the *E. coli* cells and reduce the non-specific analyte retention in the microfluidic channel. Kim *et al* [111] functionalized the surface of PLGA-b-PEG-NH_2 diblock copolymer electrospun nanofibers with amine groups to immobilize the lysozyme enzyme and covalently attach the RGD peptides. Sasikala *et al* [112] fabricated electrospun poly (D,L-lactide-co-glycolide) (PLGA) nanofiber matrix which is incorporated with the iron oxide nanoparticles (IONPs), and functionalized with 2-(3,4-dihydroxyphenyl)ethylamine (dopamine) in order to conjugate the borate which contains anti-cancer drug bortezomib. A simple immersion method was used to functionalize the surface of polydopamine. The magnetic nanofibers were aimed to use in the treatment of hyperthermia and achieve a tumor-triggered drug release.

Functionalization of nanostructured surfaces via coatings of functional, biocompatible and conducting polymers deposited by vapor deposition processes has been demonstrated [69, 113]. Ozaydin-Ince *et al* [114] synthesized 1D surface-imprinted polymeric nanotubes for specific recognition of biomolecules. The imprinted nanotubes were synthesized by first coating the pores of sacrificial membranes with immobilized proteins and subsequently removing the template and proteins to release the nanotubes (figure 8).

Polymeric structures with smart chemistries are developed to enhance the *in vivo* performance and to improve the release of the drugs in response to stimuli. Functionalization can be achieved with methods including click chemistry, thiol-ene (thiol-yne) reaction, catalyst-mediated controlled drug conjugation, pH-sensitive groups, redox-sensitive groups, enzyme-sensitive functionalities, photo-responsive functionalities, light-based photo-responsive materials, thermosensitive polymers and zwitterionic polymers [11, 115].

Functionalization of conducting polymer nanostructures is especially important in biosensing applications due to higher sensitivity and better selectivity. Functionalization can be performed via several different methods [98, 116], during or after polymerization steps. Functional groups can be conjugated in advance with the tube forming amphiphiles or with their analogous molecules in prefunctionalization.

Luo *et al* [117] fabricated functionalized PEDOTs by using a template-free electropolymerization method on an indium-oxide substrate to identify the relation between functional groups, nanostructures and electrical properties. They used alkyl and perfluorocarbon groups to fabricate a superhydrophobic and self-cleaning surface.

Post-polymerization functionalization is another technique, which is performed after polymerization. A specific molecule with a functional group covalently binds to another functional group on the surface of the substrate polymer [98]. However, most of the time electrosynthesis of conducting polymers with reactive entities is required to graft the functional groups. PEDOT nanotubes were functionalized post-polymerization with polydopamine, which is a biocompatible polymer with the ability to achieve a required therapeutic drug release profile.

Shimizu *et al* [118] and his group used a coassembly mixture of functionalized amphiphiles and tube-forming mother amphiphiles to functionalize the outer surfaces of self-organized nanotubes. Inner surfaces could be functionalized by electrostatic interaction and as a result, nanotubes with tunable diameters and high protein loading capacities could be synthesized.

Organic materials such as polyaniline (PANI) and polypyrrole (PPy) are more compatible with biomolecules than the inorganic materials [119]. Bangar *et al* [120] investigated the biofunctionalization of PPy nanowires by using glutaraldehyde (GA) and N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC), which have been employed widely for the covalent immobilization of biomolecules. They compared GA and EDC chemistries to establish an efficient covalent surface bio-functionalization route, and they found that EDC is the most effective chemistry; thus, it was used to functionalize a single PPy nanowire surface with cancer antigen (CA 125) antibody to produce a nano-immunosensor for CA 125 biomarker detection. Also, surface immobilization of monoclonal antibodies (mAbs) using EDC can be used in biosensor applications with PANI nanowires [119, 121]. Lee *et al* [119, 121] used PANI nanowires to develop a biosensor with surface immobilization by using mAbs of target proteins ethyl-3-(3-dimethyaminopropyl) carbodiimide (EDC), and N-Hydroxysuccinimde (NHS). Surface modifications are essential for electrospun nanofibers to improve the *in vivo* usage for biomedical applications such as tissue engineering, wound dressing, immobilized enzymes and drug

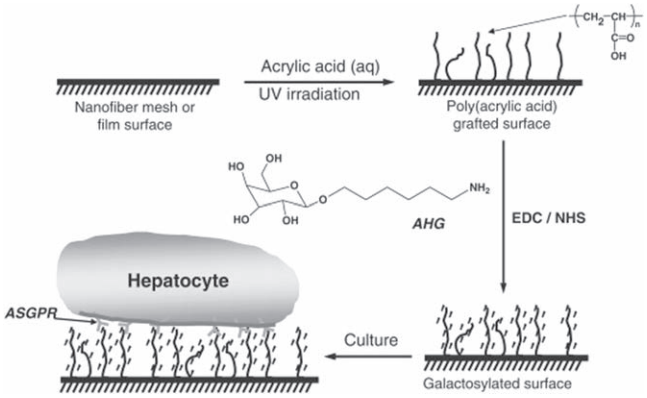

Figure 9. Surface modification for galactose conjugation to PCLPEEP nanofiber mesh and spin-cast film. Poly(acrylic acid) (PAAc) was grafted on to the scaffold surface by photo-polymerization. Reprinted from [123] Copyright 2004, with permission from Elsevier.

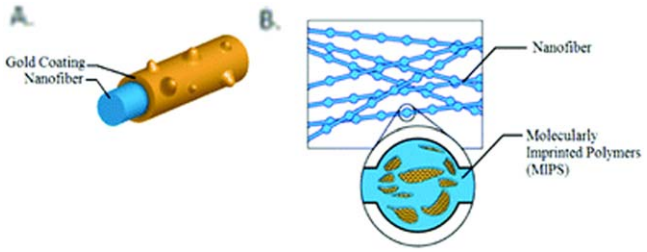

Figure 10. Gold coated electrospun nanofibers (left) with encapsulated molecularly imprinted polymers (right) for improved analyte detection. Reproduced from [124] with permission of The Royal Society of Chemistry.

delivery applications [122]. In figure 9, nanofibers were functionalized to have mechanical stability for tissue engineering applications [123].

Polyaniline, chitosan, poly (vinyl alcohol), polypyrrole and polylactic acid electrospun nanofibers have been used in electrodes to increase the surface area within electrochemical sensors. Nanofibers demonstrated a significant increase in the functionalized surface area on the electrodes, when compared to other sensors thus resulting in larger linear ranges and lower limits of detection [124]. Molecularly imprinted polymers (MIPs) within nanofibers were studied to obtain highly sensitive systems. Figure 10 represents the incorporation of MIPs within nanofiber networks in order to construct high sensitivity systems.

For detection of biological molecules the functionalized conducting nanotubes should maintain their biorecognition properties and be stable [99]. For magnetic manipulation of polymer nanotubes, Newland *et al* [34] fabricated a photo-crosslinkable polymer utilizing atom transfer radical polymerization, which can be crosslinked within the pores of an AAO template, and functionalized these nanotubes with IONPs. Doxorubicin was uploaded into polymer nanotubes so that magnetically directed polymer nanotubes can provide doxorubicin delivery *in vitro*. The dual functionality of the nanotubes can be used to combine hyperthermia and drug delivery applications. Xie *et al* [15], fabricated PEDOT nanowire devices for protein detection applications. PEDOT nanowires were assembled with carboxylic acid side chain functional groups (poly (EDOT-COOH)) to allow bioconjugation via an electric field-assisted method. The functionalized PEDOT nanowires demonstrated p-type field-effect transistor (FET) properties and could be used to detect target protein molecules.

4. Applications

4.1. Drug delivery

There is a significant research interest in the field of nanostructures in drug delivery systems [125]. The development of the drug delivery systems with nanostructures changed the traditional pharmaceutical systems because of their advantages such as; controlled and sustained delivery to increase the efficiency and to decrease the side effects of the drug, prevention from any chemical reactions between the drug and the system for preserving drug well, minimizing the wastage of drug for maximizing the availability at specific site for lengthened amount of time and increasing the solubility of insufficiently water soluble drugs [17, 18, 126, 127].

Nanotubes, which have unique electronic, thermal and structural characteristics provide a promising approach for biosensing and efficient drug delivery for detection and treatment of various diseases [18, 128].

Nanotubes can efficiently protect the drug during the delivery process against denaturation and degradation. In addition, drug loading efficiencies are higher due to their large inner volumes [129]. High loading efficiencies of the nanotubes allow administration of lower dosages of the drug in targeting specific cancer cells, enabling the delivery of chemotherapeutic agents with definitive structural characteristics better than conventional methods [130, 131].

Stimuli responsive polymers are polymeric systems that respond to changes in their environment by undergoing physical or chemical changes which are significantly beneficial for drug delivery applications. Ability to trigger the response of the drug carrier system enables the delivery system at the target site and prevents premature delivery [58].

1D drug delivery systems of stimuli responsive polymers combine the functionalities of responsive polymers with the advantages of cylindrical shapes and therefore, have attracted significant attention in the recent years [4, 58].

Armagan *et al* [71] synthesized, via templated iCVD, externally activated, pH and temperature responsive, release rate tunable and stable coaxial nanotubes with layers of poly(N-isopropylacrylamide), poly(methacrylic acid) and poly(hydroxyethyl methacrylate) to optimize and control the release of macromolecules. By changing the pH and the temperature of the environment they could tune the release rate and prolonged the release by including a hydrogel based inner layer. The release rates were calculated to be 0.089 and 0.13 min^{-1} for a single layer pMAA and pNIPAAm nanotubes however by combining two stimuli systems, release rates ranging between 0.052 and 0.134 min^{-1} were obtained. The release rate of the coaxial nanotubes reached its maximum value of 48.9% when

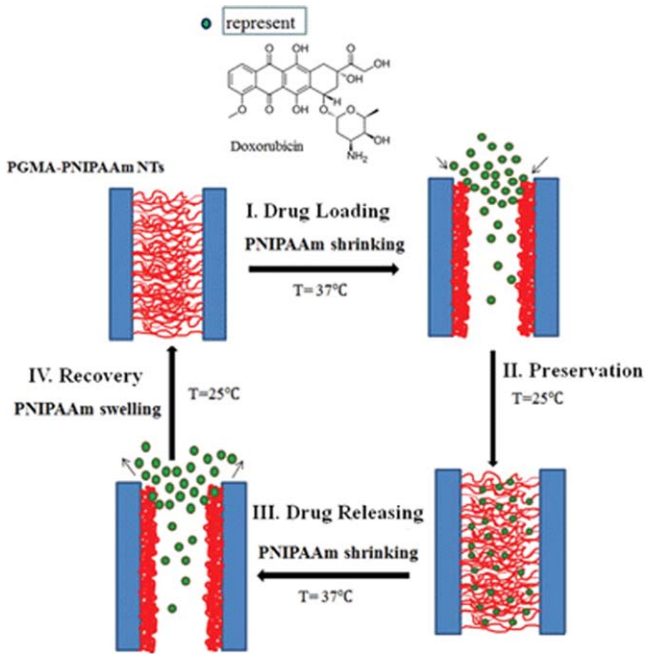

Figure 11. Thermo-responsive loading-release mechanism of Doxorubicin from PGMA-PNIPAAm nanotubes (I) Drug Loading: PGMA-PNIPAAm nanotubes were loaded with Doxorubicin at 37 °C (II) Preservation: the drug was preserved inside the nanotubes at 25 °C. (III) Drug releasing: the drug was released when the nanotubes were heated to 37 °C. (IV) Recovery: nanotubes were cooled to 25 °C to retain their initial shape. Reproduced from [35] with permission of The Royal Society of Chemistry. CC-BY 3.0.

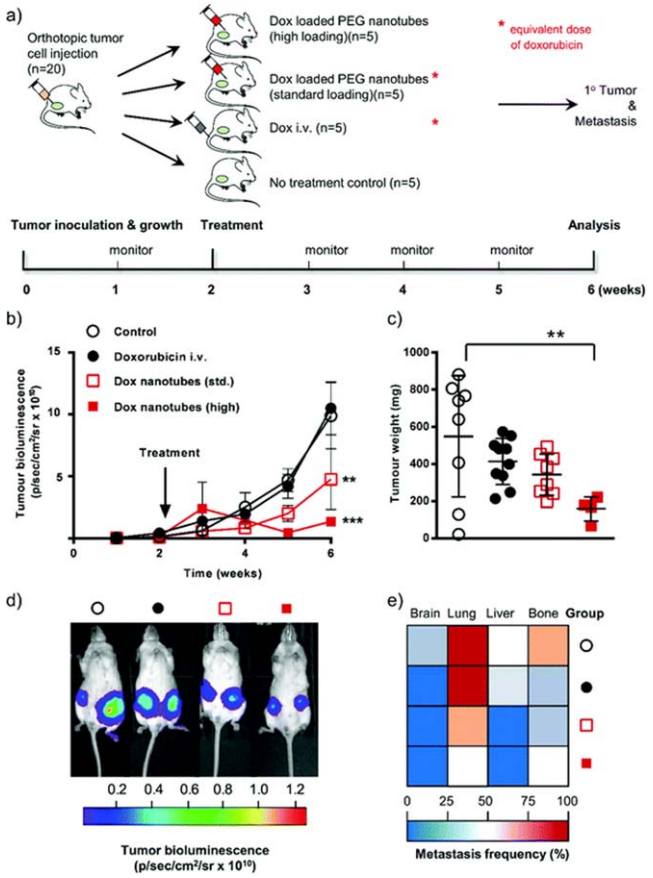

Figure 12. (a) Monitored tumor inoculation and growth over time. (b) Measurements of tumor bioluminesence with and without the nanotubes. (c) Effect of drug delivery via nanotubes on the tumor weight change. (d) Tumor bioluminesce after treatment with and without the nanotubes. (e) Metastasis frequency of different organs and tissues, reproduced from [33] with permission of The Royal Society of Chemistry. CC-BY 3.0.

the dye loading was performed at 25 °C and release at 40 °C, both at pH neutral environments. It was concluded that the release percentages of the nanotubes did not reach values as high as 50% because of the hydrophilic nature of the loaded dye. Hydrophilic dye molecules entrapped in the polymer mesh of the hydrophilic nanotubes and did not contribute to loading and release processes.

Chen *et al* [35] produced thermo-responsive polyglycidyl methacrylate nanotubes with inner walls functionalized by p(N-isopropyl acrylamide) for doxorubicin release where the nanotubes were cut by sonication-induced scission method for intracellular delivery (figure 11). The reversible closing/opening gating mechanism was activated by controlling the temperature. The system allowed enhanced loading and sustained release of the drug at 37 °C when the pNIPAAm was shrinked and the system preserved the doxorubicin inside at 25 °C with negligible release. As the temperature was increased to 37 °C, 67.47% of the drug was released after 11 h.

Newland *et al* [33] synthesized cytocompatible poly ethylene glycol (PEG) based soft and flexible nanotubes using the photopolymerization technique. Figure 12 shows the doxorubicin release from the nanotubes and the tumor growth analysis. At the end of the study, the equivalent quantity of doxorubicin delivered locally through the PEG nanotubes showed lower tumor growth than conventional injection method. Compared to the untreated controls, tumor weight was decreased substantially from 549 ± 326 mg to 414 ± 124 mg with PEG nanotubes that were loaded with the 'standard' dose of doxorubicin.

The use of electrospun fibers as drug carriers has also been investigated in the recent years [55, 132]. As a new system for delivering ketoprofen which is a non-steroidal anti-inflammatory drug, electrospun fibers were developed [61]. The fibers were synthesized from a biodegradable polymer, polycaprolactone (PCL), a non-biodegradable polymer, polyurethane (PU) or from the blends of the two. The results demonstrated that the release rates of different type of fibers were comparable and the amount of drug released from fibers increased with temperature. Furthermore, the blending polycaprolactone with polyurethane, improved the mechanical properties of polycaprolactone fibers.

Mu *et al* [63] solved the stability problem of the cancer drug cis-diamminediiodoplatinum (cis-DIDP) by loading it into Poly(ε-caprolactone) (PCL) nanofibers. This approach overcame the dissociation or premature interaction of cis-DIDP with other molecular groups and the toxicity of the drug is highly reduced due to encapsulation by the nanofibers. Tipduangta *et al* [60] mixed two partially miscible polymer blends; PVPK90 and HPMCAS to improve the tuneability of the physicochemical and mechanical properties of the drug-loaded fibers to release two different drugs to different desired

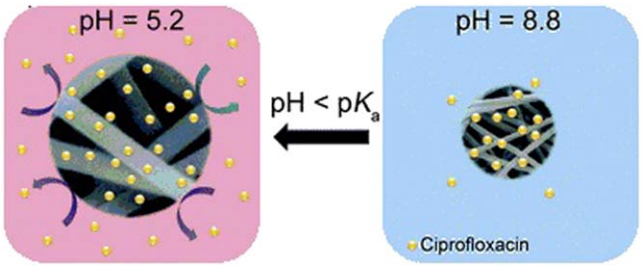

Figure 13. The release mechanism of Ciprofloxacin loaded p(VBA-co-VBTAC) nanofibers due to environmental pH change. Encapsulated drug is released when the pH is adjusted to 5.2, a value lower than pKa of VBA. Reproduced from [134] with permission of The Royal Society of Chemistry.

target sites. This also helped to develop controlled drug release formulations for which the release rate can be adjusted by changing the polymer ratio of the mixture. The release profile of the fiber was observed to be a burst release from phases rich in PVP and a slower, more continuous release from phases rich in HPMCAS.

Slemming-Adamsen *et al* [133] developed an easy one-step nanofiber production process which contains synthesizing and crosslinking with only electrospinning to create cross-linked PNIPAM/gelatin electrospun nanofibers, which exhibited thermo-responsive swelling/deswelling behavior. They demonstrated the release of the encapsulated anti-cancer drug doxorubicin (DOX) from the fibers, with an encapsulation efficiency of 91%, at the target temperature. Demirci *et al* [134], on the other hand, synthesized poly(4-vinylbenzoic acid-co-(ar-vinylbenzyl) trimethylammonium chloride) [poly(VBA-co-VBTAC)] nanofibers via reversible addition-fragmentation chain transfer polymerization. Ciprofloxacin was encapsulated by pH-responsive poly(VBA-co-VBTAC) nanofibers via electrospinning and the release of the drug could be controlled by adjusting the pH of the environment. The loading efficiency was calculated to be 93.4% ± 3.4%. Release studies performed at different pH conditions showed that, a 30 min initial burst release period was followed by a sustained release period of 240 min in acidic medium and 480 min in neutral or basic media. The percentage release of the drug in the initial burst release period increased with pH as a result of enhanced molecular interactions (figure 13).

Kim *et al* [135] produced smart hyperthermia nanofibers with an anti-cancer drug doxorubicin (DOX) and magnetic nanoparticles (MNPs), which generate heat and release the drug in response to an alternating magnetic field (AMF) for the induction of skin cancer apoptosis. The nanofibers consisted of chemically-cross-linkable temperature-responsive polymer, Poly (NIPAAm- co -HMAAm), MNPs and the drug. MNPs, acted as a trigger for the release of drugs. It was observed from the anti-cancer effect tests that 70% of human melanoma cells died in only 5 min of AMF application to loaded nanofibers. In addition, chemically crosslinked nanofiber mesh facilitated a switchable change in the drug release ratio in response to the generated heat from the AMF stimulation of MNPs, which induces the deswelling of the nanofiber (figure 14).

Conductive nanotubes, have attracted certain attention in drug delivery because of their controllable chemical and

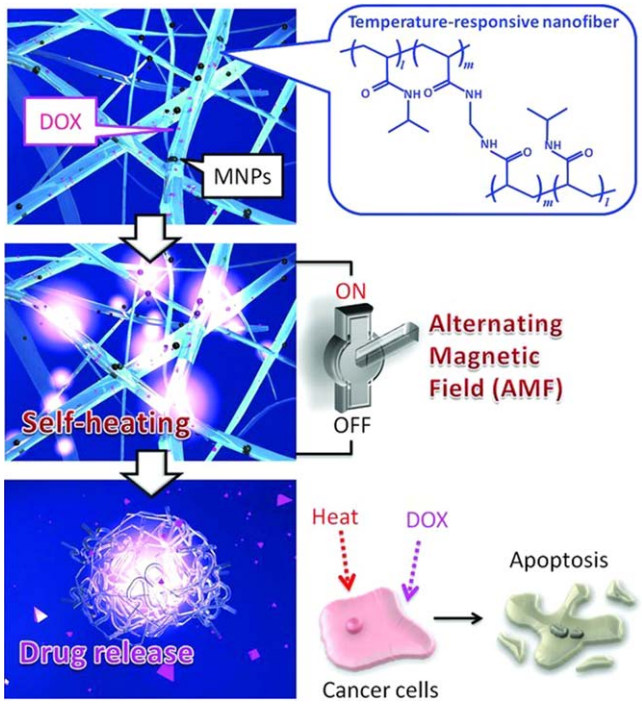

Figure 14. Release mechanism of smart hyperthermia nanofibers loaded with DOX in response to AMF. When AMF is turned on, MNPs produce enough heat to activate the drug release. Produced heat and DOX release lead to the apoptosis of cancer cells. [135] John Wiley & Sons. Copyright © 2013 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

electrochemical properties, easy processability and unique electrical properties [11, 26, 136]. They are used for their reversible electrochemical response of contraction and expansion during oxidation-reduction cycle. This induced volume change is expected to favor the controlled release of different types of drugs. For instance, conductive nanotubes are used in drug delivery systems for their reversible electro-chemical response characteristic to achieve an improved control over the delivery system. This characteristic provides little influence on drug activity, controlled release rate and a more reliable release and non-release state for the drug [11].

Abidian *et al* [128] hypothesized that PEDOT nanotubes can be used to deliver small quantities of bioactive species and this task was achieved by actively actuating the drug-loaded nanotubes with an electric field. PLGA was deliberated as the template polymer for the template of PEDOT nanotubes. In the figure 15, the demonstration of dexamethasone release from these nanotubes is presented. A significant amount of mass increase was witnessed in the released dexamethasone after the electrical excitations of 1 V applied at five specific time periods which were marked by the circled data points.

Through functionalization of the nanofiber surfaces, utilization of these nanostructures as drug delivery devices can be enhanced due to the additional functionalities the nanofibers attain.

Nanofiber surfaces can be easily functionalized by chemical or physical vapor deposition methods to change the chemical or mechanical properties of the surfaces [137]. For hierarchical materials design, the ability to coat the surfaces of

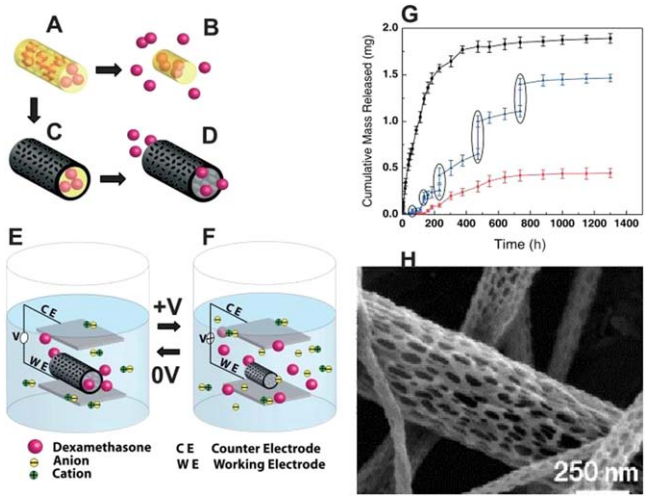

Figure 15. (A) Dexamethasone loaded PLGA fibers. (B) Drug release due to hydrolytic degradation of PLGA fibers. (C) Dexamethasone release is slowed down because of the electrochemical deposition of PEDOT around the electrospun PLGA fiber (D). (E) Neutral electrical condition of PEDOT coated electrospun PLGA fibers. (F) Effect of the external electrical stimulation on the release of dexamethasone from the PEDOT coated electrospun PLGA fibers. (G) Mass release of dexamethasone at different conditions. (H) SEM image of the electrospun PLGA fibers, [128] John Wiley & Sons. Copyright © 2006 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

the nanofibers with polymer films is important, as the coatings can extend the range of material properties available, such as surface wettability. Superhydrophobic surfaces with a water contact angle of more than 150° can be achieved by coating submicron electrospun fiber mats with hydrophobic polymer poly(perfluoroalkyl ethyl methacrylate) (PPFEMA) with iCVD [69].

Chiellini *et al* [138] synthesized bioerodible poly(maleic anhydride-alt-2-methoxyethyl vinyl ether) by electrospinning for anti-inflammatory drug, diclofenac sodium, and human serum albumin (HSA) release. They showed that separate loading of these two components resulted in uniform distribution of fibers, whereas simultaneous loading caused heterogeneous distribution. By the erosion of polymeric nanocarriers, complete release of agents was achieved within 7 h.

Nanofibers in which some agents and structures are embedded are also used for drug delivery to improve the release kinetics. Mickova *et al* [139] embedded liposomes into coaxial polyvinyl alcohol/poly-ε-caprolactone nanofibers to enhance the short half-life, low stability and ineffective retention of liposomes. For delivery and enzymatic activity studies, FITC-Dextran and horseradish peroxide (HRP) were used. Coaxial electrospun fibers with embedded liposomes improved the release kinetics of the drug compared to the delivery systems without the liposomes due to increased stimulation of MSC proliferation. The fluorescence spectroscopy analysis showed that FITC-Dextran release was extended by adding liposomes to the coaxial nanofibers. The sample without the liposomes had an intense initial burst release (60.6%) that was subsequently followed by a slow release. On the other hand, the nanofibers with liposomes had a release profile which started with a lower initial burst release (20%) followed by a sustained release. The release halftime of the first sample was 20 h and for the second sample it was 112 h.

In another study, Wang *et al* [140] developed a novel system for controlled drug delivery of multiple drugs using chitosan nanoparticles/PCL composite fibers, achieving the release of rhodamine B and naproxen. Drug loaded polymeric nanoparticles were embedded in the core part of the PCL fibers forming chainlike structure. The release of multiple drugs was successfully achieved by these core/shell nanofibers. It was seen that both with rhodamine B and naproxen, a controlled release was achieved when its compared to conventional drug release. The cumulative drug release of Naproxen was 60.5% and was %18.1 for rhodamine-b after 72 h.

Meng *et al* [141] fabricated fenbufen (FBF) loaded PLGA and PLGA/gelatin nanofibers by electrospinning. Increasing the gelatin concentration increased the hydrophilicity of the composite material leading to the burst release of drug from the PLGA/gelatin fibers. In addition, crosslinking ratio of these fibers affected the initial burst release and with the change of the pH value of the buffer solution the release rate of FBF changed. Besides, the physical characteristics of fibers changed with different pH values. At higher pH, fibers switched to a more rubbery state and at lower pH, fibers shifted to a more glassy state. This physical characteristic confirmed that the diffusion of the drug changed with different mobilities of distinct fiber states, leading to pH dependent release profile.

Another biocompatible hybrid nanofiber delivery system was produced by Mendes *et al* [142]. They synthesized chitosan/phospholipid nanofibers for transdermal vitamin B12, curcumin, and diclofenac delivery and demonstrated that the release profiles of these hybrid nanofibers were determined by the solubility property of the loaded drug solution. It was determined from the release studies that different amounts of phospholipids changed the release profiles of generated electrospun hybrid nanofibers. Two different profiles with different amounts of phospholipids showed a similar burst release within the first day. However at the end of 7 d, phospholipid intensive fibers showed 100% release whereas fibers with low concentration of phospholipids showed 90% release of vitamin B12.

Besides the nanotube and nanofibers, nanorods and nanowires are also used for drug delivery applications. Pelras *et al* [143] synthesized pH-responsive nanorod-like carriers by grafting from approach from poly(ethylene glycol) methyl ether methacrylate (PEGMA) and vinyl benzaldehyde (VBA) monomers for doxorubicin (DOX) release. These pH sensitive drug carriers showed faster drug release in acidic conditions compared to neutral pH environments. It was observed that 60% of conjugated DOX was released at pH 5.0 while only 15% was released in the same time period at pH 7.4.

4.2. Biosensor

Development of biosensors for the detection of proteins or enzymes using nanostructures featuring electrochemical

characteristics has attracted much interest [144]. The sensors' performance depends on the kind of nanostructures biomaterials interact with. Sensitivity of the sensors can be significantly increased by utilizing high aspect ratio 1D nanostructures as the sensing components. The high surface area of these nanostructures provides larger interaction areas with the biomolecules to be detected, improving the sensitivity of the device [99, 145]. Because of its high sensitivity, biocompatibility and ease of preparation, polymer nanofibers, nanotubes and nanorods have been used widely in biosensors [77, 146, 147].

Chitosan which is a biodegradable and biocompatible polymer has been widely used in biosensing applications. Especially their ability to immobilize enzymes are exploited and nanofibers of chitosan and chitin are integrated often in biosensors. Furthermore, the amino and the hydroxyl groups of the chitosan enable easy crosslinking of the chitosan with different substrates [124, 148].

Gomathi *et al* [149] fabricated chitosan nanofiber/gold nanoparticle composite for cholesterol measurements in human serum samples. The synthesized chitosan nanofibers/gold nanoparticles (CSNFs/AuNPs) which were immobilized with cholesterol oxidase (ChOx) showed a good response to cholesterol at a concentration range of 1–45 M, and improved sensitivity (1.02 A/M). Poly (vinyl alcohol) nanofibers have also been used in amperometric biosensors for glucose detection by immobilizing the glucose oxidase enzyme on the fibers. Sensor electrodes that were modified with the nanofibers exhibited rapid response with high sensitivity. Results indicated that, electrospun nanofibers had efficient response rate and thus could be used as enzymatic electrodes by integrating with biosensors [150]. In another study, chitosan/PVA electrospun nanofibers have been used to immobilize the enzyme lipase using a coupling reagent, glutaraldehyde [151], resulted in improved thermal and pH stability compared to free enzymes. Electrospun polylactic acid (PLA) nanofibers were also used to fabricate biotinylated nanofiber membranes with a large number of binding sites for streptavidin. These membranes with biotinylated nucleic acid probes were then used in biosensors for detection of synthetic *E. coli* DNA [152]. Biosensing is commonly used to pursue the biological activity of target spices. In order to obtain continuously reliable signals, immobilizing transducer material on sensing platforms is vital. Since conducting polymers are more compatible with biological systems, they have attracted more attention compared to ceramics and metals. Conducting polymer nanowires, with conductivities that can be modulated up to 15 orders of magnitude via changing the monomer/dopant ratio, are widely used in biosensors, due to their unique chemical, electronic and mechanical properties [26, 77, 98].

For chemical and biological sensors, using conducting polymers have additional advantages since the interaction between analytes has an impact on the redox and doping states of conducting polymers that results in the development on the current, resistance or electrochemical potential [136]. Chang *et al* [41] synthesized conductive polyaniline nanotubes for an ultrasensitive electrochemical nucleic acid

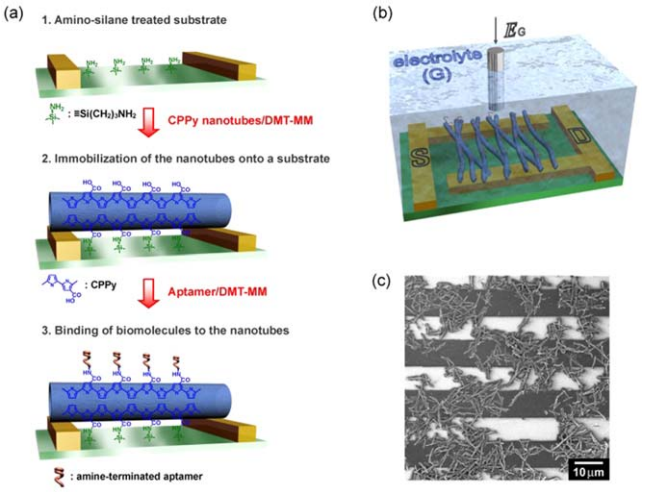

Figure 16. (a) Nanotubes immobilized on aminosilane-treated substrates and biomolecule binding on the nanotubes, (b) the FET configuration of the CPPy nanotube sensor platform (c) FE-SEM image of the CPPy nanotubes deposited on the microelectrode substrate. (c) [157] John Wiley & Sons. Copyright © 2008 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

biosensor. PANI nanotube array had a significant effect, which was used as a signal enhancement element enabling the DNA biosensor to detect a target oligonucleotide at a concentration as low as 1.0 fM (300 zmol of target molecules). Also, the biosensor showed a good differentiation between the target oligonucleotide and mismatched oligonucleotides, which were at a concentration of 35.79 fM. The developed biosensor can find potential application in a single nucleotide polymorphism analysis and single mutation detection. Ekanayake *et al* [153] fabricated polypyrrole (PPy) nanotube array deposited on a Pt plated nano-porous alumina substrate which was immobilized with glucose oxidase (GOx) enzyme. This method led to efficient loading of the enzyme and provided an increase in the surface area which resulted in the increase of the enzyme absorption capacity. This unique technique enabled a decrease in the required enzyme amount for fabrication and increased the performance of the biosensor. Tolani *et al* [154] synthesized poly (pyrrolepropylic acid) nanowires and took real-time dynamic sensing measurements of fluorescence-tagged human serum albumin. Kochana *et al* [155] achieved to obtain a long-term stable tyrosinase biosensor by using PPy nanowires. The developed biosensor showed good analytical characteristics in biosensor sensitivity, linear range, reproducibility, and reproducibility. García-Aljaroa *et al* [156] fabricated PPy nanowire-based biosensor with extremely high sensitivity for the detection of bacterial spores. Even at low concentrations, PPy-based chemiresistive biosensor was able to detect *Bacillus globigii* for the immobilization of antibodies.

Yoon *et al* [157] demonstrated fabrication of ion gated field effect (FET) sensors for label free electrochemical protein detection by using polypyrrole nanotubes attached on the electrode surface via the interactions between the surface amino groups of the electrode and the carboxyl groups of the nanotubes (figure 16).

Aussawasathien *et al* [158] synthesized PANI/PS (polystyrene) composite nanofibers, with large surface area and good electrical conductivity, via electrospinning for detection of H_2O_2. H_2O_2 plays an important role in the detection of glucose as it is a byproduct of the reaction between glucose and oxygen in the presence of glucose oxidase enzyme. With the inclusion of nanofibers in the sensor, the sensitivity increased 20 times due to higher enzyme immobilization.

Conductive polyaniline (PANI) nanowires are widely used for biosensor applications due to conductivity of polyaniline that can be changed by a few orders of magnitude by tuning the electrochemical potential and pH of the solution [159]. Lee *et al* [119] fabricated single site-specific, ultrasensitive polyaniline (PANI) nanowire biosensors with good specificity for the detection of cardiac biomarkers such as myoglobin (Myo), cardiac troponin I (cTnI), creatine kinase-MB (CK-MB) and b-type natriuretic peptide (BNP). Also, due to the good biocompatibility of single PANI nanowire-based biosensors can be applied for various studies as cancer or other diseases. They integrated single PANI nanowire-based biosensors in microfluidic devices for the detection of very low concentrations of Myo (100 pg ml^{-1}), cTnI (250 fg ml^{-1}), CK-MB (150 fg ml^{-1}), and BNP (50 fg ml^{-1}), with a short response time (few minutes).

Lee *et al* [121], synthesized a single PANI nanowire by an electrochemical growth method allowing the nanowire growth between the electrodes. Functionalization of the nanowires with mAbs enabled detection of the target proteins immunoglobulin G (IgG) and myoglobin (Myo) with high sensitivity and specificity. The biosensor showed a fast response (few seconds) and low detection limits of 3 fg ml^{-1} for IgG and 1.4 fg ml^{-1} for Myo. Fabricated biosensor can also be used for cardiac markers, which are used in the diagnosis and risk stratification, and for the detection of other proteins.

5. Conclusion

One-dimensional polymeric nanostructures, i.e. nanotubes, nanofibers, nanowires, hold great promise in different bioapplications due to their high surface area-to-volume ratios, biocompatible nature, surface functional groups and ability to control their response to external stimuli.

The performance of the 1D nanostructures depends significantly on their structure and properties which can be controlled by tuning the synthesis process. Among many different synthesis processes of 1D nanostructures, the most commonly used methods fall under the categories of solution -based and vapor- phase synthesis techniques. Highly correlated and aligned nanostructures can be fabricated via templated methods, which employ sacrificial, porous templates to assist the growth of the nanostructures. As a result, the synthesized nanostructures have the same dimensions as the pores of the templates. Synthesis can be significantly simplified by employing template-free synthesis methods which rely on self-assembly, however, these methods suffer from poor control of the morphology and alignment of the nanostructures. Electrospinning provides improved control on the dimensions even in the absence of templates. Vapor-phase synthesis techniques employ templates and operate under all-dry conditions, eliminating the toxic solvents from the process. Lithographic methods are also widely used for 1D nanostructure synthesis, allowing the control of the position and the dimensions of the nanostructures.

Bioapplications of these 1D nanostructures require active interactions between their surfaces and the environment, which can be achieved by functionalization of surfaces with specific biomolecules. These functionalized nanostructures find applications in various areas due to their tunable dimensions and functionalities. Among various bioapplications, drug delivery and biosensing applications especially benefit from the high surface area to volume ratios of these functionalized nanostructures. As new synthesis and functionalization techniques are developed, the application areas of these nanostructures will further diversify.

Acknowledgments

This work was supported by the TUBITAK (The Scientific and Technological Research Council of Turkey) Support Program for Scientific and Technological Research Projects (Grant 114M165).

ORCID iDs

Gozde Ozaydin Ince https://orcid.org/0000-0003-3255-4940

References

[1] Farokhzad O C, Langer R, Excellence C N and Engineering C 2009 Impact of nanotechnology on drug delivery *Am. Chem. Soc. Nano* **3** 16–20
[2] Martin C R and Mitchell D T 2008 Peer reviewed: nanomaterials in analytical chemistry *Anal. Chem.* **70** 322A–7A
[3] Wallace G G, Higgins M J, Moulton S E and Wang C 2012 Nanobionics: the impact of nanotechnology on implantable medical bionic devices *Nanoscale* **4** 4327–47
[4] Goldberg M, Langer R and Jia X 2007 Nanostructured materials for applications in drug delivery and tissue engineering *J. Biomater. Sci. Polym. Ed.* **18** 241–68
[5] Tran H D, Li D and Kaner R B 2009 One-dimensional conducting polymer nanostructures: bulk synthesis and applications *Adv. Mater.* **21** 1487–99
[6] Svirskis D, Travas-Sejdic J, Rodgers A and Garg S 2010 Electrochemically controlled drug delivery based on intrinsically conducting polymers *J. Control. Release* **146** 6–15
[7] Aghabegi Moghanjoughi A, Khoshnevis D and Zarrabi A 2016 A concise review on smart polymers for controlled drug release *Drug Deliv. Transl. Res.* **6** 333–40

[8] Malhotra B D, Chaubey A and Singh S P 2006 Prospects of conducting polymers in biosensors *Anal. Chim. Acta* **578** 59–74

[9] Liechty W B, Kryscio D R, Slaughter B V and Peppas N A 2010 Polymers for drug delivery systems *Annu. Rev. Chem. Biomol. Eng.* **1** 149–73

[10] Yoon H and Jang J 2009 Conducting-polymer nanomaterials for high-performance sensor applications: issues and challenges *Adv. Funct. Mater.* **19** 1567–76

[11] Das T K and Prusty S 2012 Review on conducting polymers and their applications *Polym.—Plast. Technol. Eng.* **51** 1487–500

[12] Xia B Y, Yang P, Sun Y, Wu Y, Mayers B, Gates B, Yin Y, Kim F and Yan H 2003 One-dimensional nanostructures: synthesis, characterization, and applications *Adv. Mater.* **15** 353–89

[13] Lieber C M 1998 One-dimensional nanostructures: chemistry, physics & applications *Solid State Commun.* **107** 607–16

[14] Uppalapati D, Boyd B J, Garg S, Travas-Sejdic J and Svirskis D 2016 Conducting polymers with defined micro- or nanostructures for drug delivery *Biomaterials* **111** 149–62

[15] Xie H, Luo S C and Yu H H 2009 Electric-field-assisted growth of functionalized poly(3,4- ethylenedioxythiophene) nanowires for label-free protein detection *Small* **5** 2611–7

[16] LaVan D A, McGuire T and Langer R 2003 Small-scale systems for *in vivo* drug delivery *Nat. Biotechnol.* **21** 1184–91

[17] Singh A 2017 Recent review on nanofiber for drug delivery systems *World J. Pharm. Res.* **6** 611–31

[18] Purvya M and Meena M 2011 A review on role of prakriti in aging *AYU (Int. Q. J. Res. Ayurveda)* **32** 20–4

[19] Chou S F, Carson D and Woodrow K A 2015 Current strategies for sustaining drug release from electrospun nanofibers *J. Control. Release* **220** 584–91

[20] Xue J, Xie J, Liu W and Xia Y 2017 Electrospun Nanofibers: new concepts, materials, and applications *Acc. Chem. Res.* **50** 1976–87

[21] Cheng F, Tao Z, Liang J and Chen J 2008 Template-directed materials for rechargeable lithium-ion batteries *Chem. Mater.* **20** 667–81

[22] Wei Z, Zhang Z and Wan M 2002 Formation mechanism of self-assembled polyaniline micro/nanotubes *Langmuir* **18** 917–21

[23] Yang Y and Wan M 2002 Chiral nanotubes of polyaniline synthesized by a template-free method *J. Mater. Chem.* **12** 897–901

[24] Choi S J and Park S M 2000 Electrochemical growth of nanosized conducting polymer wires on gold using molecular templates *Adv. Mater.* **12** 1547–9

[25] Zhong W, Liu S, Chen X, Wang Y and Yang W 2006 High-yield synthesis of superhydrophilic polypyrrole nanowire networks *Macromolecules* **39** 3224–30

[26] Long Y Z, Li M M, Gu C, Wan M, Duvail J L, Liu Z and Fan Z 2011 Recent advances in synthesis, physical properties and applications of conducting polymer nanotubes and nanofibers *Prog. Polym. Sci.* **36** 1415–42

[27] Ma Y, Zhang J, Zhang G and He H 2004 Polyaniline nanowires on Si surfaces fabricated with DNA templates *J. Am. Chem. Soc.* **126** 7097–101

[28] Nickels P, Dittmer W U, Beyer S, Kotthaus J P and Simmel F C 2004 Polyaniline nanowire synthesis templated by DNA *Nanotechnology* **15** 1524–9

[29] Watson S M D, Galindo M A, Horrocks B R and Houlton A 2014 Mechanism of formation of supramolecular DNA-templated polymer nanowires *J. Am. Chem. Soc.* **136** 6649–55

[30] Li G and Zhang Z 2004 Synthesis of dendritic polyaniline nanofibers in a surfactant gel *Macromolecules* **37** 2683–5

[31] Martin C R 1995 Template synthesis of electronically conductive polymer nanostructures *Acc. Chem. Res.* **28** 61–8

[32] Steinhart M, Wehrspohn R B, Gösele U and Wendorff J H 2004 Nanotubes by template wetting: a modular assembly system *Angew. Chem., Int. Ed.* **43** 1334–44

[33] Newland B, Taplan C, Pette D, Friedrichs J, Steinhart M, Wang W and Werner C 2018 Soft and flexible poly(ethylene glycol) nanotubes for local drug delivery *Nanoscale* **10** 8413–21

[34] Newland B, Leupelt D, Zheng Y, Thomas L S V, Werner C, Steinhart M and Wang W 2015 Magnetically controllable polymer nanotubes from a cyclized crosslinker for site-specific delivery of doxorubicin *Sci. Rep.* **5** 1–13

[35] Chen G, Chen R, Zou C, Yang D and Chen Z S 2014 Fragmented polymer nanotubes from sonication-induced scission with a thermo-responsive gating system for anti-cancer drug delivery *J. Mater. Chem.* B **2** 1327–34

[36] Chen J T, Zhang M and Russell T P 2007 Instabilities in nanoporous media *Nano Lett.* **7** 183–7

[37] Schlitt S, Greiner A and Wendorff J H 2008 Cylindrical polymer nanostructures by solution template wetting *Macromolecules* **41** 3228–34

[38] Yoon H, Chang M and Jang J 2006 Sensing behaviors of polypyrrole nanotubes prepared in reverse microemulsions: effects of transducer size and transduction mechanism *J. Phys. Chem.* B **110** 14074–7

[39] Han M G and Foulger S H 2005 1-Dimensional structures of poly(3,4-ethylenedioxythiophene) (PEDOT): a chemical route to tubes, rods, thimbles, and belts *Chem. Commun.* **1** 3092–4

[40] Pan L, Pu L, Shi Y, Song S, Xu Z, Zhang R and Zheng Y Synthesis of polyaniline nanotubes with a reactive template of manganese oxide *Adv. Mater.* **19** 461–4

[41] Chang H, Yuan Y, Shi N and Guan Y 2007 Electrochemical DNA biosensor based on conducting polyaniline nanotube array *Anal. Chem.* **79** 5111–5

[42] Martín J, Maiz J, Sacristan J and Mijangos C 2012 Tailored polymer-based nanorods and nanotubes by 'template synthesis': from preparation to applications *Polymer* **53** 1149–66

[43] Cao B Y, Kong J, Xu Y, Yung K L and Cai A 2013 Polymer nanowire arrays with high thermal conductivity and superhydrophobicity fabricated by a nano-molding technique *Heat Transfer Eng.* **34** 131–9

[44] Huang J, Virji S, Weiller B H and Kaner R B 2003 Polyaniline nanofibers: facile synthesis and chemical sensors *J. Am. Chem. Soc.* **125** 314–5

[45] de Moel K, Alberda van Ekenstein G O R, Hijland H, Polushkin E, Brinke G, Mäki-Ontto R and Ikkala O 2001 Polymeric nanofibers prepared from self-organized supramolecules *Chem. Mater.* **13** 4580–3

[46] Yoon H 2013 Current trends in sensors based on conducting polymer nanomaterials *Nanomaterials* **3** 524–49

[47] Huang J and Kaner R B 2004 A general chemical route to polyaniline nanofibers *J. Am. Chem. Soc.* **126** 851–5

[48] Huang J and Kaner R B 2004 Nanofiber formation in the chemical polymerization of aniline: a mechanistic study *Angew. Chem., Int. Ed.* **43** 5817–21

[49] Wang Y, Jing X and Kong J 2007 Polyaniline nanofibers prepared with hydrogen peroxide as oxidant *Synth. Met.* **157** 269–75

[50] Chiou N R and Epstein A J 2005 Polyaniline nanofibers prepared by dilute polymerization *Adv. Mater.* **17** 1679–83

[51] Li D, Huang J and Kaner R B 2009 ChemInform Abstract: polyaniline nanofibers: a unique polymer nanostructure for versatile applications *ChemInForm* **40** 135–45

[52] Janošević A, Ćirić-Marjanović G, Marjanović B, Holler P, Trchová M and Stejskal J 2008 Synthesis and

characterization of conducting polyaniline 5-sulfosalicylate nanotubes *Nanotechnology* **19** 135606
[53] Feng J, Yan W and Zhang L 2009 Synthesis of polypyrrole micro/nanofibers via a self-assembly process *Microchim. Acta* **166** 261–7
[54] Fan H, Yu X, Liu Y, Shi Z, Liu H, Nie Z and Jin Z 2015 Folic acid-polydopamine nanofibers show enhanced ordered-stacking via π–π interactions *Soft Matter* **11** 4621–9
[55] Al-Enizi A, Zagho M and Elzatahry A 2018 Polymer-based electrospun nanofibers for biomedical applications *Nanomaterials* **8** 259
[56] Schiffman J D and Schauer C L 2008 A review: electrospinning of biopolymer nanofibers and their applications *Polym. Rev.* **48** 317–52
[57] Hrib J, Sirc J, Hobzova R, Hampejsova Z, Bosakova Z, Munzarova M and Michalek J 2015 Nanofibers for drug delivery—incorporation and release of model molecules, influence of molecular weight and polymer structure *Beil. J. Nanotechnol.* **6** 1939–45
[58] Chen S, Li R, Li X and Xie J 2018 Electrospinning: an enabling nanotechnology platform for drug delivery and regenerative medicine *Adv. Drug Deliv. Rev.* **132** 188–213
[59] Khajavi R and Abbasipour M 2012 Electrospinning as a versatile method for fabricating coreshell, hollow and porous nanofibers *Sci. Iran* **19** 2029–34
[60] Tipduangta P, Belton P, Fábián L, Wang L Y, Tang H, Eddleston M and Qi S 2015 Electrospun polymer blend nanofibers for tunable drug delivery: the role of transformative phase separation on controlling the release rate *Mol. Pharm.* **13** 25–39
[61] Kenawy E R, Abdel-Hay F I, El-Newehy M H and Wnek G E 2009 Processing of polymer nanofibers through electrospinning as drug delivery systems *Mater. Chem. Phys.* **113** 296–302
[62] Yoshimoto H, Shin Y M, Terai H and Vacanti J P 2003 A biodegradable nanofiber scaffold by electrospinning and its potential for bone tissue engineering *Biomaterials* **24** 2077–82
[63] Mu C and Wu Q 2017 Electrospun poly(ε-caprolactone) composite nanofibers with controlled release of cis-diamminediiodoplatinum for a higher anticancer activity *Nanoscale Res. Lett.* **12**
[64] Kenawy E R, Bowlin G L, Mansfield K, Layman J, Simpson D G, Sanders E H and Wnek G E 2002 Release of tetracycline hydrochloride from electrospun poly(ethylene-co-vinylacetate), poly(lactic acid), and a blend *J. Control. Release* **81** 57–64
[65] Shin H J, Lee C H, Cho I H, Kim Y J, Lee Y J, Kim I A, Park K D, Yui N and Shin J W 2006 Electrospun PLGA nanofiber scaffolds for articular cartilage reconstruction: mechanical stability, degradation and cellular responses under mechanical stimulation *in vitro J. Biomater. Sci. Polym. Ed.* **17** 103–19
[66] González E and Frey M W 2017 Synthesis, characterization and electrospinning of poly(vinyl caprolactam-co-hydroxymethyl acrylamide) to create stimuli-responsive nanofibers *Polymer* **108** 154–62
[67] Ohkawa K, Cha D, Kim H, Nishida A and Yamamoto H 2004 Electrospinning of chitosan *Macromol. Rapid Commun.* **25** 1600–5
[68] Zhu Y, Feng L, Xia F, Zhai J, Wan M and Jiang L 2007 Chemical dual-responsive wettability of superhydrophobic PANI-PAN coaxial nanofibers *Macromol. Rapid Commun.* **28** 1135–41
[69] Baxamusa S H, Im S G and Gleason K K 2009 Initiated and oxidative chemical vapor deposition: a scalable method for conformal and functional polymer films on real substrates *Phys. Chem. Chem. Phys.* **11** 5227–40
[70] Alf M E *et al* 2009 Chemical vapor deposition of conformal, functional, and responsive polymer films *Adv. Mater.* **22** 1993–2027
[71] Armagan E and Ozaydin Ince G 2015 Coaxial nanotubes of stimuli responsive polymers with tunable release kinetics *Soft Matter* **11** 8069–75
[72] Ozaydin-Ince G, Gleason K K and Demirel M C 2011 A stimuli-responsive coaxial nanofilm for burst release *Soft Matter* **7** 638–43
[73] Ozaydin-Ince G and Gleason K K 2010 Tunable conformality of polymer coatings on high aspect ratio features *Chem. Vapor Depos.* **16** 100–5
[74] Ozaydin Ince G, Demirel G, Gleason K K and Demirel M C 2010 Highly swellable free-standing hydrogel nanotube forests *Soft Matter* **6** 1635–9
[75] Im S G, Kusters D, Choi W, Baxamusa S H, van de Sanden M C M and Gleason K K 2008 Conformal coverage of poly(3,4- ethylenedioxythiophene) Films with tunable nanoporosity *ACS Nano* **2** 1959–67
[76] Balkan A, Armagan E and Ince G O 2017 Synthesis of coaxial nanotubes of polyaniline and poly(hydroxyethyl methacrylate) by oxidative/initiated chemical vapor deposition *Beil. J. Nanotechnol.* **8** 872–82
[77] Wang J and Zhang D 2013 One-dimensional nanostructured polyaniline: syntheses, morphology controlling, formation mechanisms, new features , and applications *Adv. Polym. Technol.* **32** 323–68
[78] Back J W, Lee S, Hwang C R, Chi C S and Kim J Y 2011 Fabrication of conducting PEDOT nanotubes using vapor deposition polymerization *Macromol. Res.* **19** 33–7
[79] Lee K J, Oh J H, Kim Y and Jang J 2006 Fabrication of photoluminescent dyes/poly(acrylonitrile) coaxial nanotubes using vapor deposition polymerization *Chem. Mater.* **18** 5002–8
[80] Jang J and Oh J H 2004 A facile synthesis of polypyrrole nanotubes using a template-mediated vapor deposition polymerization and the conversion to carbon nanotubes *Chem. Commun.* **4** 882–3
[81] Kwon O S, Park S J, Park H, Kim T, Kang M, Jang J and Yoon H 2012 Kinetically controlled formation of multidimensional poly(3,4-ethylenedioxythiophene) nanostructures in vapor-deposition polymerization *Chem. Mater.* **24** 4088–92
[82] Demirel M C, Boduroglu S, Cetinkaya M and Lakhtakia A 2007 Spatially organized free-standing poly(p-xylylene) nanowires fabricated by vapor deposition *Langmuir* **23** 5861–3
[83] Choi W, An T and Lim G 2011 Fabrication of conducting polymer nanowires *Nanowires—Implementations Applications* (London: IntechOpen)
[84] Nuxoll E 2013 BioMEMS in drug delivery *Adv. Drug Deliv. Rev.* **65** 1611–25
[85] Song G, Li X, Li P, Peng Z, She X, Li J and Sun J 2012 Assembly of one-dimensional polymer nanostructure arrays by photolithographic approaches *J. Porous Mater.* **19** 195–9
[86] Li X, Wang Y, Song G, Peng Z, Li P, Lin Q, Zhang N, Wang Z and Duan X 2009 Fabrication of patterned polystyrene nanotube arrays in an anodic aluminum oxide template by photolithography and the multiwetting mechanism *J. Phys. Chem.* B **113** 12227–30
[87] Li X, Han P, Song G, Peng Z, Yu Y, Feng S, Zhou C and Li M 2015 Assembly of polyamide 6 nanotube arrays with ordered patterns and the crystallization behavior *Mater. Lett.* **141** 157–60
[88] Werake L K, Story J G, Bertino M F, Pillalamarri S K and Blum F D 2005 Photolithographic synthesis of polyaniline nanofibres *Nanotechnology* **16** 2833

[89] Jiang L, Dong H and Hu W 2011 Controlled growth and assembly of one-dimensional ordered nanostructures of organic functional materials *Soft Matter* **7** 1615–30

[90] Muanchan P, Suzuki S, Kyotani T and Ito H 2016 One-dimensional polymer nanofiber arrays with high aspect ratio obtained by thermal nanoimprint method *Polym. Eng. Sci.* **57** 214–23

[91] Xia Y and Whitesides G M 1998 Soft Lithography *Annu. Rev. Mater. Sci.* **28** 153–84

[92] Zhang F, Nyberg T and Inganäs O 2002 Conducting polymer nanowires and nanodots made with soft lithography *Nano Lett.* **2** 1373–7

[93] Jiang Y, Tang N, Zhou C, Han Z, Qu H and Duan X 2018 A chemiresistive sensor array from conductive polymer nanowires fabricated by nanoscale soft lithography *Nanoscale* **10** 20578–86

[94] Tang N, Jiang Y, Qu H and Duan X 2017 Conductive polymer nanowire gas sensor fabricated by nanoscale soft lithography *Nanotechnology* **28**

[95] Pisignano D, Maruccio G, Mele E, Persano L, Di Benedetto F and Cingolani R 2005 Polymer nanofibers by soft lithography *Appl. Phys. Lett.* **87** 1–3

[96] Lim J-H and Mirkin C A 2002 Electrostatically driven dip-pen nanolithography of conducting polymers *Adv. Mater.* **14** 1474–7

[97] Maynor B W, Filocamo S F, Grinstaff M W and Liu J 2002 Direct-writing of polymer nanostructures: poly(thiophene) nanowires on semiconducting and insulating surfaces *J. Am. Chem. Soc.* **124** 522–3

[98] Wanekaya A K, Chen W, Myung N V and Mulchandani A 2006 Nanowire-based electrochemical biosensors *Electroanalysis* **18** 533–50

[99] Mulchandani A and Myung N V 2011 Conducting polymer nanowires-based label-free biosensors *Curr. Opin. Biotechnol.* **22** 502–8

[100] Yoo H S, Kim T G and Park T G 2009 Surface-functionalized electrospun nanofibers for tissue engineering and drug delivery *Adv. Drug Deliv. Rev.* **61** 1033–42

[101] Kolewe K W, Dobosz K M, Rieger K A, Chang C C, Emrick T and Schiffman J D 2016 Antifouling electrospun nanofiber mats functionalized with polymer zwitterions *ACS Appl. Mater. Interfaces* **8** 27585–93

[102] Braun E, Eichen Y, Sivan U and Ben-Yoseph G 1998 DNA-templated assembly and electrode attachment of a conducting silver wire *Nature* **391** 775–8

[103] Hopkins D S, Pekker D, Goldbart P M and Bezryadin A 2005 Quantum interference device made by DNA templating of superconducting nanowires *Science* **308** 1762–5

[104] Dong L, Hollis T, Connolly B A, Wright N G, Horrocks B R and Houlton A 2007 DNA-templated semiconductor nanoparticle chains and wires *Adv. Mater.* **19** 1748–51

[105] Sánchez-Mosteiro G *et al* 2006 DNA-based molecular wires: multiple emission pathways of individual constructs *J. Phys. Chem.* B **110** 26349–53

[106] Keren K, Berman R S, Buchstab E, Sivan U and Braun E 2003 DNA-templated carbon nanotube field-effect transistor *Science* **302** 1380–2

[107] Guan J, Yu B and Lee L J 2007 Forming highly ordered arrays of functionalized polymer nanowires by dewetting on micropillars *Adv. Mater.* **19** 1212–7

[108] Asatekin A, Barr M C, Baxamusa S H, Lau K K S, Tenhaeff W, Xu J and Gleason K K 2010 Designing polymer surfaces via vapor deposition *Mater. Today* **13** 26–33

[109] Wang J 2009 Biomolecule-functionalized nanowires: fom nanosensors to nanocarriers *ChemPhysChem* **10** 1748–55

[110] Matlock-Colangelo L, Coon B, Pitner C L, Frey M W and Baeumner A J 2015 Functionalized electrospun poly(vinyl alcohol) nanofibers for on-chip concentration of *E. coli* cells *Anal. Bioanal. Chem.* **408** 1327–34

[111] Kim T G and Park T G 2006 Surface functionalized electrospun biodegradable nanofibers for immobilization of bioactive molecules *Biotechnol. Prog.* **22** 1108–13

[112] Sasikala A R K, Unnithan A R, Yun Y H, Park C H and Kim C S 2016 An implantable smart magnetic nanofiber device for endoscopic hyperthermia treatment and tumor-triggered controlled drug release *Acta Biomater.* **31** 122–33

[113] Gupta M, Kapur V, Pinkerton N M and Gleason K K 2008 Initiated chemical vapor deposition (iCVD) of conformal polymeric nanocoatings for the surface modification of high-aspect-ratio pores *Chem. Mater.* **20** 1646–51

[114] Ince G O, Armagan E, Erdogan H, Buyukserin F, Uzun L and Demirel G 2013 One-dimensional surface-imprinted polymeric nanotubes for specific biorecognition by initiated chemical vapor deposition (iCVD) *ACS Appl. Mater. Interfaces* **5** 6447–52

[115] Ramasamy T, Ruttala H B, Gupta B, Poudel B K, Choi H G, Yong C S and Kim J O 2017 Smart chemistry-based nanosized drug delivery systems for systemic applications: a comprehensive review *J. Control. Release* **258** 226–53

[116] Bangar M A, Chen W, Myung N V and Mulchandani A 2010 Conducting polymer 1-dimensional nanostructures for FET sensors *Thin Solid Films* **519** 964–73

[117] Luo S C, Sekine J, Zhu B, Zhao H, Nakao A and Yu H H 2012 Polydioxythiophene nanodots, nonowires, nano-networks, and tubular structures: the effect of functional groups and temperature in template-free electropolymerization *ACS Nano* **6** 3018–26

[118] Shimizu T, Minamikawa H, Kogiso M, Aoyagi M, Kameta N, Ding W and Masuda M 2014 Self-organized nanotube materials and their application in bioengineering *Polym. J.* **46** 831–58

[119] Lee I, Luo X, Huang J, Cui X T and Yun M 2012 Detection of cardiac biomarkers using single polyaniline nanowire-based conductometric biosensors *Biosensors* **2** 205–20

[120] Bangar M A, Shirale D J, Chen W, Myung N V and Mulchandani A 2009 Single conducting polymer nanowire chemiresistive label-free immunosensor for cancer biomarker *Anal. Chem.* **81** 2168–75

[121] Lee I, Luo X, Cui X T and Yun M 2011 Highly sensitive single polyaniline nanowire biosensor for the detection of immunoglobulin G and myoglobin *Biosens. Bioelectron.* **15** 3297–302

[122] Liang D, Hsiao B S and Chu B 2007 Functional electrospun nanofibrous scaffolds for biomedical applications *Adv. Drug Deliv. Rev.* **59** 1392–412

[123] Chua K-N, Lim W-S, Zhang P, Lu H, Wen J, Ramakrishna S, Leong K W and Mao H-Q 2004 Stable immobilization of rat hepatocyte spheroids on galactosylated nanofiber scaffold *Biomaterials* **26** 2537–47

[124] Matlock-Colangelo L and Baeumner A J 2012 Recent progress in the design of nanofiber-based biosensing devices *Lab Chip* **12** 2612–20

[125] Zelikin A N, Ehrhardt C and Healy A M 2016 Materials and methods for delivery of biological drugs *Nat. Chem.* **8** 997–1007

[126] Ali A and Ahmed S 2018 A review on chitosan and its nanocomposites in drug delivery *Int. J. Biol. Macromol.* **109** 273–86

[127] Soppimath K S, Aminabhavi T M, Kulkarni A R and Rudzinski W E 2001 Biodegradable polymeric nanoparticles as drug delivery devices *J. Controlled Release* **70** 1–20

[128] Abidian M R, Kim D H and Martin D C 2006 Conducting-polymer nanotubes for controlled drug release *Adv. Mater.* **18** 405–9

[129] Chen G 2012 Nanotube-based controlled drug delivery *Pharm. Anal Acta.* **3** 2153–435

[130] Senapati S, Mahanta A K, Kumar S and Maiti P 2018 Controlled drug delivery vehicles for cancer treatment and their performance *Signal Transduct. Target. Ther.* **3** 1–19
[131] Parhi P, Mohanty C and Sahoo S K 2012 Nanotechnology-based combinational drug delivery: an emerging approach for cancer therapy *Drug Discovery Today* **17** 1044–52
[132] Pillay V, Dott C, Choonara Y E, Tyagi C, Tomar L, Kumar P, Du Toit L C and Ndesendo V M K 2013 A review of the effect of processing variables on the fabrication of electrospun nanofibers for drug delivery applications *J. Nanomater.* **2013** 789289
[133] Slemming-Adamsen P, Song J, Dong M, Besenbacher F and Chen M 2015 *In situ* cross-linked PNIPAM/Gelatin nanofibers for thermo-responsive drug release *Macromol. Mater. Eng.* **300** 1226–31
[134] Demirci S, Celebioglu A, Aytac Z and Uyar T 2014 PH-responsive nanofibers with controlled drug release properties *Polym. Chem.* **5** 2050–6
[135] Kim Y J, Ebara M and Aoyagi T 2013 A smart hyperthermia nanofiber with switchable drug release for inducing cancer apoptosis *Adv. Funct. Mater.* **23** 5753–61
[136] Lu X, Zhang W, Wang C, Wen T C and Wei Y 2011 One-dimensional conducting polymer nanocomposites: synthesis, properties and applications *Prog. Polym. Sci.* **36** 671–712
[137] Yu D-G, Zhu L-M, White K and Branford-White C 2009 Electrospun nanofiber-based drug delivery systems *Health* **01** 67–75
[138] Piras A M, Chiellini F, Chiellini E, Nikkola L and Ashammakhi N 2008 New multicomponent bioerodible electrospun nanofibers for dual-controlled drug release *J. Bioact. Compat. Polym.* **23** 423–43
[139] Mickova A, Buzgo M, Benada O, Rampichova M, Fisar Z, Filova E, Tesarova M, Lukas D and Amler E 2012 Core/Shell nanofibers with embedded liposomes as a drug delivery system *Biomacromolecules* **13** 952–62
[140] Wang Y, Wang B, Qiao W and Yin T 2010 A novel controlled release drug delivery system for multiple drugs based on electrospun nanofibers containing nanoparticles *J. Pharm. Sci.* **99** 4805–11
[141] Meng Z X, Xu X X, Zheng W, Zhou H M, Li L, Zheng Y F and Lou X 2010 Preparation and characterization of electrospun PLGA/gelatin nanofibers as a potential drug delivery system *Colloids Surf.* B **84** 97–102
[142] Mendes A C, Gorzelanny C, Halter N, Schneider S W and Chronakis I S 2016 Hybrid electrospun chitosan-phospholipids nanofibers for transdermal drug delivery *Int. J. Pharm.* **510** 48–56
[143] Pelras T, Duong H T T, Kim B J, Hawkett B S and Müllner M 2017 A 'grafting from' approach to polymer nanorods for pH-triggered intracellular drug delivery *Polymer* **112** 244–51
[144] Hangarter C M, Bangar M, Mulchandani A and Myung N V 2010 Conducting polymer nanowires for chemiresistive and FET-based bio/chemical sensors *J. Mater. Chem.* **20** 3131–40
[145] Anish Kumar M, Jung S and Ji T 2011 Protein biosensors based on polymer nanowires, carbon nanotubes and zinc oxide nanorods *Sensors* **11** 5087–111
[146] Ramakrishna S, Fujihara K, Teo W-E, Yong T, Ma Z and Ramaseshan R 2006 Electrospun nanofibers: solving global issues *Mater. Today* **9** 40–50
[147] Verma N and Bhardwaj A 2015 Biosensor technology for pesticides—a review *Appl. Biochem. Biotechnol.* **175** 3093–119
[148] de Lima F, Lucca B G, Barbosa A M J, Ferreira V S, Moccelini S K, Franzoi A C and Vieira I C 2010 Biosensor based on pequi polyphenol oxidase immobilized on chitosan crosslinked with cyanuric chloride for thiodicarb determination *Enzyme Microb. Technol.* **47** 153–8
[149] Gomathi P, Ragupathy D, Choi J H, Yeum J H, Lee S C, Kim J C, Lee S H and Ghim H D 2011 Fabrication of novel chitosan nanofiber/gold nanoparticles composite towards improved performance for a cholesterol sensor *Sensors Actuators* B **153** 44–9
[150] Ren G, Xu X, Liu Q, Cheng J, Yuan X, Wu L and Wan Y 2006 Electrospun poly(vinyl alcohol)/glucose oxidase biocomposite membranes for biosensor applications *React. Funct. Polym.* **66** 1559–64
[151] Huang X J, Ge D and Xu Z K 2007 Preparation and characterization of stable chitosan nanofibrous membrane for lipase immobilization *Eur. Polym. J.* **43** 3710–8
[152] Li D, Frey M W and Baeumner A J 2006 Electrospun polylactic acid nanofiber membranes as substrates for biosensor assemblies *J. Membr. Sci.* **279** 354–63
[153] Ekanayake E M I M, Preethichandra D M G and Kaneto K 2007 Polypyrrole nanotube array sensor for enhanced adsorption of glucose oxidase in glucose biosensors *Biosens. Bioelectron.* **23** 107–13
[154] Tolani S B, Craig M, Delong R K, Ghosh K and Wanekaya A K 2009 Towards biosensors based on conducting polymer nanowires *Anal. Bioanal. Chem.* **393** 1225–31
[155] Kochana J, Hnida K, Sulka G, Knihnicki P, Kozak J and Gilowska A 2015 Application of polypyrrole nanowires for the development of a tyrosinase biosensor *Chem. Pap.* **69** 1130–5
[156] García-Aljaro C, Bangar M A, Baldrich E, Muñoz F J and Mulchandani A 2010 Conducting polymer nanowire-based chemiresistive biosensor for the detection of bacterial spores *Biosens. Bioelectron.* **25** 2309–12
[157] Yoon H, Kim J, Lee N, Kim B and Jang J 2008 A novel sensor platform based on aptamer-conjugated polypyrrole nanotubes for label-free electrochemical protein detection *ChemBioChem* **9** 634–41
[158] Aussawasathien D, Dong J H and Dai L 2005 Electrospun polymer nanofiber sensors *Synth. Met.* **154** 37–40
[159] Song E and Choi J-W 2013 Conducting polyaniline nanowire and its applications in chemiresistive sensing *Nanomaterials* **3** 498–523