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Review

Conducting polymers with defined micro- or nanostructures for drug delivery

Dedeepya Uppalapati [a], Ben J. Boyd [b, c], Sanjay Garg [d], Jadranka Travas-Sejdic [e, f], Darren Svirskis [a, *]

[a] School of Pharmacy, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland 1023, New Zealand
[b] Drug Delivery, Disposition, and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville Campus), Victoria 3052, Australia
[c] ARC Centre of Excellence in Convergent Bio-Nano Science and Technology, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville Campus), Victoria 3052, Australia
[d] School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia, 5001, Australia
[e] Polymer Electronics Research Centre, School of Chemical Sciences, Faculty of Science, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand
[f] MacDiarmid Institute for Advanced Materials and Nanotechnology, University of Auckland, Auckland 1142, New Zealand

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ABSTRACT

Conducting polymers (CPs) are redox active materials with tunable electronic and physical properties. The charge of the CP backbone can be manipulated through redox processes, with accompanied movement of ions into and out of the polymer to maintain electrostatic neutrality. CPs with defined micro- or nanostructures have greatly enhanced surface areas, compared to conventionally prepared CPs. The resulting high surface area interface between polymer and liquid media facilities ion exchange and can lead to larger and more rapid responses to redox cycling. CP systems are maturing as platforms for electrically tunable drug delivery. CPs with defined micro- or nanostructures offer the ability to increase the amount of drug that can be delivered whilst enabling systems to be finely tuned to control the extent and rate of drug release. In this review, fabrication approaches to achieve CPs with micro- or nanostructure are outlined followed by a detailed review and discussion of recent advances in the application of the materials for drug delivery.

1. Introduction

Conducting polymers (CPs) are organic materials which possess metal-like electrical properties while retaining the mechanical properties and processability of conventional polymers [1]. These remarkable materials were discovered in 1977, which led to the Nobel Prize in chemistry being awarded to Shirakawa, McDiarmid and Heeger in 2000 [2]. The conductivity and reversible redox nature of CPs is attributed to the alternating double and single bonds with carbons in Sp^2 hybridization. The delocalized π-electrons form a conjugated backbone which renders the materials conductivity through charge mobilization [3]. Polypyrrole (PPy) [4], polythiophene [5] and its derivative poly(3,4-ethylenedioxythiophene) (PEDOT) [6], polyaniline (PANI) [7], alongside poly(*p*-phenylene vinylene) [8] and its derivatives are the most widely explored CPs. Since their discovery, CPs have been used for various applications including electrochromics, light emitting diodes, field effect transistors, energy storage devices and in biomedical applications for bio sensing, at neural interfaces and for drug delivery [9–19] CPs with defined micro- or nanostructures are exciting materials for biomedical applications due to their increased surface area offering enhanced responsiveness, reduced impedance, and high charge transfer capacity.

CPs with defined micro- or nanostructures are commonly synthesized chemically or electrochemically using a hard template [6] or soft template [20] to direct polymerization, or without a template by selecting appropriate polymerization conditions [21,22]. On alteration of the redox state of CPs, there are accompanied changes to the charge, volume, molecular permeability and hydrophobic/hydrophilic balance. These changes can be exploited to tune the release rate of drugs [23,24]. Electrically tunable delivery systems based on CPs have been reported for anionic drugs

* Corresponding author.
E-mail address: d.svirskis@auckland.ac.nz (D. Svirskis).

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(glutamate, salicylate, dexamethasone sodium phosphate (DexP)) [25–27], cationic drugs (dopamine, chlorpromazine, and risperidone) [28–30] and neutral drugs (*N*-methyl phenothiazine and progesterone) [31,32]. The amounts of drugs currently delivered from CPs are suitable for local delivery applications [33]. However, the levels of drugs delivered must be increased to enhance the versatility of these delivery platforms to a wide range of chronic disease states, for conditions requiring systemic delivery and to extend the lifetime of these delivery systems. In addition, while the influence of electrical stimulation on drug release has been demonstrated, approaches to achieve tight control over release are required for many applications.

One approach to increase both the amount of drug delivered from CPs and their responsiveness is by synthesizing highly porous polymers with defined micro- or nanostructures [6]. In addition, CPs with defined micro- or nanostructured systems have the potential to be loaded with a high level of a drug loading and are able to achieve more controlled and efficient drug delivery compared to the unstructured CP systems [34,35]. This review focuses on the synthesis approaches to prepare electro-responsive CPs with defined micro- or nanostructures and their applications in tunable drug delivery.

2. Synthesis of CPs with defined micro- or nanostructures

CPs are oxidatively polymerized (Fig. 1) from their respective monomers, polypyrrole has been selected as a representative example. Monomers are oxidized to form radical cations, followed by a coupling reaction to form oligomers [36]. These oligomers, in turn, couple with a monomer cation or another oligomer and the chain length extends to form a polymer. Oxidation can be driven either by a chemical oxidant (chemical synthesis) or by an oxidizing potential applied through an electrode (electrochemical synthesis) [37]. Frequently electrochemical methods are favored in drug delivery as they offer finer control over the quantity and electrical properties of the final polymer by controlling the rate and amount of charge that is passed through.

Different fabrication approaches have been reported to synthesize CPs with defined micro- or nanostructures using either chemical or electrochemical polymerization approaches (Fig. 2). Template-directed polymerization relies on existing structures to guide polymer growth. This includes hard template-directed polymerization in which a hard micro- or nanostructured material is used as a template, whereas in soft template-directed polymerization, a self-assembled molecular template is used. In template-free polymerization, precise polymerization conditions are employed to manipulate the initial nucleation reactions which influence the morphology and properties of the final polymer formed [36,38,39].

2.1. Hard template-directed polymerization

Micro- or nanostructured solid materials have been used as templates to direct the polymerization of CPs. Synthesis of CP using a hard template was first explored by Martin et al. to synthesize CP

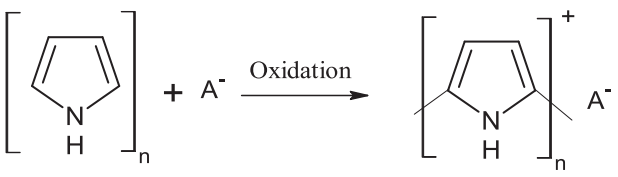

Fig. 1. Oxidative polymerization of polypyrrole (PPy).

nanofibers and tubules inside the pores of polycarbonate membranes [40]. The resulting micro- or nanostructures of CPs match the shape and diameter of the template utilized in their synthesis.

The use of hard templates is the most common approach to prepare uniform micro- or nanostructures due to convenience, simplicity, and controllability. The size and thickness of the resultant micro- or nanostructures can be controlled by the size of the template features and polymerization time. However, a drawback of hard template methods is when removal of the template is required. Post-polymerization removal of the template can be challenging and may complicate the process and destroy the fabricated nanostructures. In addition, the overall dimensions of the template restrict the amount of CP that can be produced by this method, and may limit the ability to scale up processes.

Chemical or electrochemical polymerization of CPs can be guided by hard templates. In chemical polymerization, the hard template is immersed in a solution composed of monomers, dopant, and an oxidant. When employing electrochemical polymerization, the hard template should be conductive or in contact with a conductive surface from which polymer growth begins. CPs with defined micro- or nanostructures result from polymerization within the well-defined spaces of the hard template or over existing discrete nanostructures, resulting in the structures as presented in Fig. 3. Depending on the intended application of these structured CPs, the template can be removed leaving a negative copy of the starting material [39].

2.1.1. Membranes

CPs with a range of micro- or nanostructures including tubes, wires, rods, and fibers can be polymerized in the pores or channels of membranes (Fig. 3a). The morphology of these formed structures depends on the initial template used. By controlling the polymerization time, thin-walled tubules (short polymerization times), thick-walled tubules (intermediate polymerization times) and even solid fibers (long polymerization times) can be produced within the pores of membranes. Track-etched membranes and anodized alumina are commonly used hard templates for this purpose. Track-etched membranes with diameters as low as 10 nm and pore densities of 10^9 pores cm^{-2} can be produced by irradiating high energy heavy ions onto a polycarbonate (PC) or polyethylene terephthalate (PET) membrane [41]. Polypyrrole (PPy) and polyaniline (PANI) polymerized on a PC membrane produced micro- or nanotubules preferentially due to the growth of polymer from the surface of pore walls [42–44]. The production of solid fibers can be difficult due to limited diffusion of reagents into the formed nanotubules. To synthesize solid nanofibers, Duchet et al. proposed a modified method by the successive polymerization of PPy in a PC membrane by immersing the membrane in fresh monomer and dopant solution after each polymerization step (Fig. 4) [45]. The conductivity of PANI nanotubules produced either chemically or electrochemically on a PC membrane was greater than the bulk polymer, with higher conductivities at lower tubule diameters attributed to the presence of a higher proportion of oriented polymer chains within narrow PANI tubules (>60 S cm^{-1} for tubules with diameters < 50 nm whereas conductivity fell to < 10 S cm^{-1} for tubules >200 nm in diameter) [46].

Alumina (anodized aluminum oxide-AAO) is formed on electrochemical anodic oxidation of aluminum with pore densities as high as 10^{11} pores cm^{-2} [47]. Han et al. reported that the morphology of PEDOT chemically polymerized in alumina membranes could be controlled by changing the concentration of the oxidant and polymerization temperature. They reported that at low $FeCl_3$ concentration and low temperatures, thin-walled nanotubes can be obtained. As the concentration and temperature increased the wall thickness of nanotubes increased until solid nanorods