Porous conducting polymer prepared through liquid crystal template for drug delivery

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Abstract: Unlike conventional controlled drug delivery systems where drug is released at a constant pre-programmed rate, drug release from conducting polymers (CPs) can be controlled through electrical stimuli and adjusted based on the patient’s needs. However, owing to their low drug loading capacity and limited electrical responsiveness CP systems cannot currently be applied for systemic drug delivery or to treat chronic disease. To overcome that obstacle one approach is to fabricate porous CP structures. In this work, polypyrrole (PPy) was used owing to its electrical responsiveness and biocompatibility. Liquid crystals were used as a template through which PPy was grown. Dexamethasone phosphate was loaded as a dopant into PPy during polymerisation and its release was quantified by HPLC after the removal of liquid crystal; release could be modified by electrical stimulus. This system has potential applications in conditions where required drug dosing changes with time, such as in age-related macular degeneration.

Keywords: conducting polymer; lyotropic liquid crystal; phase transition; scanning electron microscopy; SEM; small angle X-ray scattering; SAXS; polypyrrole; stimuli responsive drug delivery system.


Biographical notes: Dedeepya Uppalapati started her PhD at The University of Auckland with Dr. Darren Svirskis after completing her Masters at the National Institute of Pharmaceutical Education and Research (NIPER), Mohali, India. Her current research involves developing stimuli responsive drug delivery systems using conducting polymers. Her research interests include conducting polymers and their biomedical applications, liquid crystalline drug delivery systems and triggered drug delivery.

Ben Boyd is a Professor in Drug Delivery Sciences at Monash Institute of Pharmaceutical Sciences. His research interests include colloidal aspects of lipid-based formulation design, dendrimers as colloidal drug delivery systems, lipid based liquid crystalline drug delivery systems, non-lamellar dispersed liquid crystalline drug delivery systems, novel particulate carriers for siRNA and DNA delivery, and novel methods for characterisation of materials for drug delivery systems. He received over $7 M in research funding and published over 100 papers in peer reviewed journals. He is the winner 2011 American Association of Pharmaceutical Sciences award for Outstanding Research in Lipid Based Drug Delivery.

Jadranka Travas-Sejdic is a Professor at the School of Chemical Sciences, and Director of the Polymer Electronics Research Centre at the University of Auckland, and a Principal Investigator at the MacDiarmid Institute for Advanced Materials and Nanotechnology. Her research interests are in the fields of advanced polymeric materials for bio sensing and bioelectronics, electrically and environmentally responsive polymers and surfaces, actuators, materials for tissue engineering and nanostructured conducting polymers. She has (co)authored ca. 200 publications, including eight book chapters.

Darren Svirskis is a Pharmacist and Senior Lecturer in Pharmaceutics at the University of Auckland. His research interests are in implantable biomaterials, with both biodegradable and non-biodegradable drug delivery systems formulated with release profiles designed to match clinical requirements. He has a research focus using conducting polymers as a
platform for drug delivery. His research has demonstrated the ability of conducting polymers to control drug delivery, and how electrical stimulation can be used to modify drug release. This technology could be used for implantable drug delivery devices, where the dose could be adjusted to optimise patient benefit to side effect ratios while simultaneously ensuring treatment adherence. Currently, he is exploring biological triggers to control drug release from CP systems. He has received over $1 M in competitive research funding and published over 20 papers in peer reviewed journals. He is a Committee Member of the New Zealand local chapter of the Controlled Release Society.

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1 Introduction

Conducting polymers (CPs) are increasingly being applied to biomedical purposes including drug delivery [1], bio-sensing [2] and neural prosthetics [3,4]. CPs can achieve triggered drug delivery in response to electrical stimulus. Drug delivery from conducting polymers is often limited owing to their low drug loading capacity and limited responsiveness. To increase their loading capacity and responsiveness to electrical stimulation, strategies have been developed using hard templates, soft templates and some template-less methods to produce porous conducting polymer structures [5,6]. Among CPs, polypyrrole (PPy) is most commonly used in drug delivery owing to its conductivity, biocompatibility and ease of preparation [7]. In this study phytantriol liquid crystal was used as a soft template to prepare porous PPy films. Phytantriol is an amphiphilic lipid which self-assembles in excess water to form lyotropic liquid crystals which are thermodynamically stable [8]. It forms different phases (lamellar, cubic, hexagonal) at different lipid to water ratios and temperatures [9,10]. Using a soft template such as a phytantriol liquid crystal, through which PPy is polymerised, is advantageous owing to its simple preparation, and ability to remove the template after polymerisation without destroying the formed porous structures [11].

Dexamethasone phosphate is a steroidal anti-inflammatory and immunosuppressant drug used in chronic back of the eye conditions such as age related macular degeneration (AMD) [12]. Required dosing of dexamethasone phosphate for AMD is around 100 ng/day; this varies based on disease condition and response to drug. AMD is commonly treated by intravitreal injections of steroidal drugs, including dexamethasone, with poor treatment adherence a barrier to successful therapy. Though implantable drug delivery systems can provide sustained release of drugs to the eye, the release rates are pre-determined and cannot be altered when required. Therefore, there has been a paradigm shift from conventional implantable systems to stimuli responsive drug delivery systems [13]. Systems capable of modifying release rates of drug in response to electrical stimulus would be beneficial for systemic as well as local drug delivery purposes in chronic diseases that require changing doses of drug.

This study aimed to use a liquid crystal as a soft template through which a porous PPy could be electropolymerised capable of electrically triggered drug release.
2 Materials and methods

2.1 Materials

Pyrrole was purchased from Aldrich (Australia), vacuum distilled and stored under nitrogen at –20°C until use. p-toluene sulphonic acid monohydrate (pTS) was obtained from Aldrich, Australia. Phytantriol was obtained from DSM Nutritional Products Ltd. (Singapore) and dexamethasone phosphate was purchased from Jai Radhe Sales, India. MilliQ water was from Millipore/Millipak system with filter size 0.22 µm, ITO slides with resistance of 70–100 Ω were purchased from Delta technologies. PBS tablets were obtained from Sigma-Aldrich, Australia and each tablet when dissolved in 200 ml of MilliQ water at 25°C yields pH 7.4 and comprising 0.137 M sodium chloride, 0.0027 M potassium chloride, 0.01 M Na2HPO4 and 0.0018 M KH2PO4.

2.2 Phase diagram of phytantriol/water

To determine the phase diagram of phytantriol/water and composition of different phases of phytantriol liquid crystals, phytantriol and water were weighed accurately and heated to 75°C in Eppendorf tubes. Phytantriol was injected into the water at 75°C, and subjected to three repeat cycles of vortexing for 2 min and centrifugation for 5 min at 2800 g. The samples were then equilibrated at 37°C for 48 h [14]. After equilibration samples were heated to different temperatures from 20°C to 70°C at 10°C per min using a hot stage and viewed under cross-polarised light microscopy.

2.3 Electrochemical polymerisation of porous PPy through liquid crystal template

For the electrochemical polymerisation of PPy through the liquid crystal template, a 50 : 50 ratio of lipid and water was selected which forms bicontinuous cubic phase with excess water. Liquid crystal templated PPy growth was achieved by first dissolving 1 M pyrrole in 1 g of phytantriol (lipid phase) and 0.4 M pTS in 1 g of water (aqueous phase). The phytantriol liquid crystal was then formed by heating both lipid and aqueous phases to 75°C, injecting the lipid phase into the aqueous phase. Since pyrrole is unstable to oxygen, samples were immediately transferred onto an ITO coated glass slide which acted as the working electrode. PPy was grown electrochemically in potentiostatic mode at 0.7 V vs. an Ag/AgCl reference electrode for 1 h by keeping the working and counter electrodes (stainless steel mesh) directly in contact with the liquid crystal, without additional electrolyte (Figure 1(a)).

2.4 Scanning electron microscopy (SEM)

Samples were investigated using a Philips XL30S field emission microscope. Liquid crystal was washed away using isopropanol and the PPy samples were mounted on aluminium stubs using adhesive graphite tape to view surface morphology. Cross sectional images were obtained in a similar manner by first cryo-fracturing the films under liquid nitrogen.
2.5 Cyclic voltammetry (CV)

A three electrode setup was used to record CVs of the films. The films with liquid crystal were cycled between –1 V to +1 V (vs. Ag/AgCl (0.3 M KCl) at a rate of 10 mV/s without any additional electrolyte using an eDAQ potentiostat (model EA161) and E-corder 410 with E-Chem software (NSW, Australia).

2.6 Small angle X-ray scattering (SAXS)

Small angle X-ray scattering was performed at the SAXS/WAXS beam line at the Australian Synchrotron. Samples were placed in 96 well plates sealed with Kapton tape. The wavelength was 0.1127 nm (11 keV). The sample to detector distance was fixed to 600 mm with an exposure time of 2 s. Diffraction patterns were collected on a Pilatus 1 M detector (Dectris) and integrated using the in-house software package scatterbrain.

2.7 Drug release studies

Templated films were synthesised using the same method mentioned above except that pTS was replaced with dexamethasone phosphate for both stimulated and unstimulated films. For comparison, conventional untemplated films were polymerised from an aqueous solution containing pyrrole and dexamethasone phosphate. Four freshly prepared films were used in each of the four investigated groups, templated stimulated, templated unstimulated, untemplated stimulated and untemplated unstimulated. For stimulated drug release experiments, films were stimulated using a 3 electrode setup in PBS with a pulse of ±0.6 V, 0.5 Hz at 24, 48, 72 and 144 h for 5, 10, 10 and 60 min, respectively (Figure 1(b)). For controls, unstimulated films were observed under the same experimental conditions without any electrical stimulation. The released drug was quantified by HPLC.

3 Results and discussion

Mixtures of the amphiphilic lipid phytantriol (Figure 2(a)) and water formed different liquid crystal phases depending on the lipid to water ratio and temperature as presented in
Figure 2(b). From the phase diagram, a lipid to water ratio of 50 : 50 was selected for the electrochemical polymerisation of PPy. At this ratio the liquid crystal was in the bicontinuous cubic phase with an excess of water present which was confirmed by cross polarised light microscopy.

**Figure 2** (a) Chemical structure of phytantriol and (b) Phase diagram of phytantriol and water, L2 – inverse micellar, Lα – lamellar, H2 – reverse hexagonal, Q2 – inverse bicontinuous cubic phase

SEM was used to investigate the surface morphology and cross section of the template films after washing away the liquid crystal template with a porous structure evident. Typical PPy demonstrates a cauliflower surface morphology with a non-porous cross-section, however, the images in Figure 3 show a distinctive porous morphology on both the nodular surface (Figure 3(a)) and in cross-section (Figure 3(b)) in imitation of the liquid crystal structure [8,15].

**Figure 3** SEM images of PPy polymerised through liquid crystal: (a) surface morphology and (b) cross section

CV was used to determine the electro responsiveness of the PPy. Clear oxidation peaks at +0.4 V and reduction peaks at –0.5 V were observed indicating the conductivity and reversible electro-activity of the liquid crystal templated PPy (Figure 4). Over the
five cycles measured a change in reduction behaviour was observed; this behaviour was repeatable between samples. The CVs were recorded inside a host liquid crystal template, on repeated cycling there may have been changes to the liquid crystal nanostructure resulting in changes in ion movement across the polymer / liquid crystal interface and changes in the observed CV.

**Figure 4** CV of the porous film scanned from −1 V to +1 V at a scan rate of 10 mV/s in the liquid crystal

![Graph of CV](image)

**Figure 5** SAXS profile of (a) bicontinuous cubic phase, (b) bicontinuous cubic phase with PPy after polymerisation (see online version for colours)

![SAXS profiles](image)

SAXS was used to determine the phase of the liquid crystal before and after PPy polymerisation to investigate if PPy polymerisation induced any change in liquid crystal phase. SAXS data revealed the presence of the Pn3m space group cubic phase, with peak spacing ratios of √2, √3, √4, √6, √8 and √9. The bicontinuous cubic liquid crystal and the templated PPy in liquid crystal show no differences indicating that the addition of monomer and dopant and polymerisation had no effect on the nanostructure of the cubic phase liquid crystal (Figure 5).
Dexamethasone phosphate was loaded into the films as a dopant during electrochemical polymerisation [16]. The release was determined with and without electrical stimulus. While release was slow for the unstimulated films, the stimulated templated films demonstrated bursts of release in response to electrical stimuli (Figure 6(a)). The duration of stimulation was different at different trigger time points, and interestingly there was no significant difference in the release rate per minute ($p > 0.8$, one-way ANOVA) (Table 1). Conventional non-porous films released greater masses of drug (Figure 6(b)), this can be attributed to the more efficient polymerisation process producing more polymer. The porous films prepared through the liquid crystal template produced noticeably less polymer product compared to the non-porous films when the same polymerisation charge was passed. The reduced efficiency of polymerisation within the liquid crystal can be attributed to the limitation in diffusion of monomer and dopant.
to the working electrode where they are consumed during polymerisation. For the untemplated films electrical stimulation had only moderate effects on drug release. All the groups investigated showed a burst of release before the first stimulation point. This is typically seen from CP drug releasing systems and may be owing to diffusion driven release of drug close to the polymer/media interface. This initial burst was smaller from the template PPy systems. It is possible that a thin layer of liquid crystal remains at the PPy/media interface which reduces unstimulated release from the templated films.

<table>
<thead>
<tr>
<th>Stimulation time (h)</th>
<th>Duration of stimulation (min)</th>
<th>Rate of drug release (µg/min)</th>
</tr>
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<tbody>
<tr>
<td>24</td>
<td>5</td>
<td>2.43 ± 1.17</td>
</tr>
<tr>
<td>48</td>
<td>10</td>
<td>2.02 ± 0.75</td>
</tr>
<tr>
<td>72</td>
<td>10</td>
<td>2.35 ± 0.63</td>
</tr>
<tr>
<td>144</td>
<td>60</td>
<td>2.40 ± 0.62</td>
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4 Conclusion

A conducting polymer based stimuli responsive drug delivery system has been developed using a phytantriol cubic phase liquid crystal as a template. PPy structures with a porous morphology were imaged with SEM resembling typical liquid crystal structures. The porous PPy films formed through liquid crystal templates were electro active as evident from cyclic voltammetry. This porous system was capable of releasing bursts of dexamethasone phosphate in response to electrical stimulation. Such CP based stimuli responsive drug delivery systems offer promising advantages in conditions like age-related macular degeneration where the required drug dosing changes with time.

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References

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