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ORIGINAL PAPER

The incorporation and controlled release of dopamine from a sulfonated β–cyclodextrin–doped conducting polymer

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Abstract

Pyrrole was electropolymerised in the presence of sulfonated β–cyclodextrin to give a conducting polypyrrole film doped with the anionic cyclodextrin, PPy–sβ–CD. On reduction of the polymer film at −0.80 V vs SCE, high concentrations of dopamine (DA) were incorporated and the DA was subsequently released at a potential of 0.10 V vs SCE. Much higher levels of DA were incorporated and released at PPy–sβ–CD compared to polypyrrole films doped with smaller anions and doped with the larger para–toluene sulfonic acid. In addition to releasing higher concentrations of DA, the DA was less prone to oxidation and degradation in the presence of the sulfonated β–cyclodextrin. This was attributed to the formation of an inclusion complex between the protonated DA molecule and the anionic CD. The higher release rates were explained in terms of the immobile nature of the large CD and the high charge density with approximately 9 sulfonated groups attached to the rim of the CD cavity, which facilitated the uptake of high levels of DA. Approximately 6.0 μmol cm^{-2} of DA was released at 0.10 V vs SCE over 60 min on reducing the PPy–sβ–CD film for 30 min at −0.80 V vs SCE. Higher levels of 9.6 μmol cm^{-2} were obtained on increasing the reduction period to 60 min, while levels of 14.0 μmol cm^{-2} were achieved with thicker polymer films.

Keywords Polypyrrole · Sulfonated β–cyclodextrin · Dopamine · Controlled release · Inclusion complex

Introduction

Conducting polymers, and in particular polypyrrole, have been considered and investigated as membranes for the controlled delivery of drugs [1–7]. In addition to exhibiting biocompatible properties, polypyrrole films are responsive and they can be stimulated to uptake and release ions. This uptake and release which maintains charge neutrality is associated with the redox switching between the oxidised and the reduced states, where the polymer backbone is positively charged when oxidised and neutral when reduced. A number of studies has been reported describing the uptake and release of anionic drug molecules [1–5]. During electrochemical polymerisation, the anionic drug molecules are incorporated into the polymer film as dopants to compensate the positive charge on the oxidised polypyrrole. On application of an appropriate reduction potential, these anions are released. Likewise, to facilitate the release of cationic drug molecules, large immobile dopants are employed within the polymer and then the cations are incorporated and released on oxidation of the polypyrrole film [6, 7].

However, the drug loading capacity of polypyrrole is a limitation in its application as a drug delivery system. While an increase in polymer thickness generally gives rise to an increase in the concentration of the drug released, thicker polymer films tend to become less electroactive. More recent attempts to increase the loading and concentration of the drug, include increasing the surface area of the polymer [8] by forming various polymer nanostructures [9, 10], polymer nanoparticles/particles [11–13] or nanowires [14], fibres [15, 16], nanotubes [17] and reservoirs that can be used to load the drug [18].

Cyclodextrins (CDs) have also been considered as drug carriers due to their biocompatibility and their ability to form inclusion complexes. CDs have the potential to act as hydrophobic carriers and they can be employed to control the release of a variety of drugs. Several reviews have been published describing the applications of CDs in drug delivery systems [19, 20]. Therefore, the combination of polypyrrole and cyclodextrins is attractive in controlling the delivery of

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drug molecules and provides a way of combining the unique host–guest complexation properties of cyclodextrins with the stability, high conductivity and ease of preparation of conducting polymers. Furthermore, by employing negatively charged cyclodextrins, the CDs can be incorporated within the polymer matrix as dopants. Polypyrrole has been doped with anionic CDs to give conducting polymer matrices that exhibit cation exchange properties as the large cyclodextrin is immobile and is not lost on reduction of the polymer [21, 22]. These CD–doped polypyrrole films have been used in the electrochemical detection of dopamine [23] and urea [24, 25].

In terms of a comparison between polypyrrole and other drug delivery materials, polypyrrole is not biodegradable and while it can be formed as nanowires, nanoparticles and nanotubes [11–17], it is not suitable as a carrier to deliver drugs to specific sites in the body. For these applications biodegradable polymer nanogels [26, 27] are attracting considerable interest as they have the potential to deliver drugs to the target cells. Secondly, the release mechanism differs. Many of the hydrogel–modified materials are pH responsive [28, 29] or redox responsive, capable of responding to the presence of reducing compounds [30], while in a recent report a chitosan–based hydrogel was shown to exhibit a pH, temperature and salinity response [31]. This makes these nanogel materials interesting in terms of delivery to cancer cells. While polypyrrole is responsive to pH changes and reducing agents, electrical stimulation is normally used to release molecules from the polypyrrole films [4, 6]. However, polypyrrole is particularly suited to transdermal drug delivery applications, as an implant or as a scaffold material. For example, it has been shown to promote neurite outgrowth for potential applications as cochlear implants [32] in nerve repair [33] and in neural tissue engineering [34].

In this study, polypyrrole was formed in the presence of an anionic CD (sulfonated β–cyclodextrin (sβ–CD)) and this system was used to bind and release dopamine. Dopamine (DA) is a neurotransmitter that is linked with Parkinson's disease [35] and it was selected as a model cationic drug that is prone to decomposition. There are very few publications devoted to the controlled release of DA and instead the DA precursor, L–DOPA (L–3,4–dihydroxyphenylalanine), is employed in the management of Parkinson's disease. However, in recent years there has been a renewed interest in the release of DA, as L–DOPA has a number of undesirable effects when administered [36].

Experimental

The pyrrole monomer (98%) was obtained from Aldrich and was purified by distillation and stored in the dark at −20 °C. The sulfonated β–cyclodextrin (sβ–CD) sodium salt with a degree of substitution of 7 to 11 mol of sulfonate per mole of CD was obtained from Aldrich. This salt was purified further by dissolving the CD in a small volume of water, the sample was then connected to a Schlenk line, heated to 70 °C and dried under vacuum at a pressure of 0.01 mbar for 12 h.

The electrochemical experiments were carried out using a Solartron Model SI 1287 potentiostat. A platinum rod electrode, with a geometric surface area of 1 cm^2, was used for the deposition of polypyrrole and the successive uptake and release of DA. A saturated calomel reference electrode (SCE) and a high surface area platinum wire counter electrode (CE) were used to complete the electrochemical cell. The platinum electrodes were polished using successively smaller sized diamond polishing particles (Buehler MetaDi Monocrystalline Diamond suspension) with a final size of 1 μm, rinsed with deionised water and sonicated to give a clean and smooth surface. The surface morphology of the polymer samples was obtained using a Hitachi scanning electron microscope. The samples were sputter coated with gold using an Emitech K550x gold sputter coater prior to analysis.

Unless otherwise stated, the polymer was formed at 0.80 V vs SCE to a charge of 3.0 C in a solution containing 0.2 M pyrrole and 0.01 M sβ–CD and then polarised at −0.80 V vs SCE in 0.1 M DA with a 0.1 M Na_2SO_4 supporting electrolyte for 30 min to incorporate the DA. The polymer was transferred to deionised water and held at −0.80 V vs SCE with gentle agitation for 15 min to liberate any excess DA. The release of DA was studied on application of 0.10 V vs SCE to the polymer film in a 0.1 M Na_2SO_4 supporting electrolyte. The influence of the concentration of Na_2SO_4, the reduction period and potential on the uptake of DA were studied, while variations in the release potential and time were investigated during the release of DA. All solutions were deoxygenated with nitrogen and maintained in the dark to protect the DA from decomposition. UV–visible spectroscopy (Cary 50 UV–visible spectrometer) was used to monitor the release of the DA molecule at 280 nm. All experiments were repeated at least three times, indicated by the n value in the figure captions, and the calculated error is represented as error bars on the plots.

Results

Formation of PPy–sβ–CD

In Fig. 1(a), current–time plots are shown for the electropolymerisation of 0.20 M pyrrole in the presence of 0.01 M sβ–CD at various applied potentials. It can be seen that the steady–state current increases as the deposition potential becomes more positive, indicating a higher rate of electropolymerisation with increasing potential. These observations are in good agreement with the results recorded in simple dopant electrolytes [37]. The shape of the current–

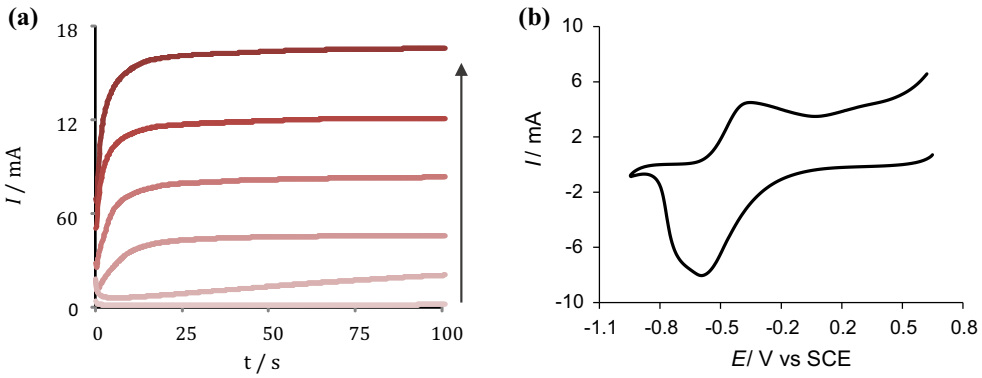

Fig. 1 **a** Current as a function of time for the formation of PPy–sβ–CD in 0.20 M pyrrole and 0.01 M sβ–CD at potentials of 0.50 V, 0.60 V, 0.70 V, 0.80 V, 0.90 V and 1.0 V vs SCE **b** Cyclic voltammogram of PPy–sβ–CD recorded in 0.1 M Na_2SO_4 at 50 mV s^{-1}

time transient is similar at the different potentials, with an initial sharp current decay, followed by a rise in the current, which depends on the applied potential, before near constant currents are observed at longer polarisation times. This is consistent with the formation of a polymer monolayer, followed by continued three–dimensional growth. The anionic sβ–CD is large and bulky with a lower diffusion coefficient compared to simple halide dopants. However, it is highly charged to give a high solution conductivity of 5 mS cm^{-1} for the 0.01 M solution. It has been reported that pyrrole forms an inclusion complex with β–cyclodextrins [38, 39] and this would reduce the rate of electropolymerisation. Using ^{1}H NMR spectroscopy, ^{1}H NMR spectra were recorded for pyrrole in the absence and presence of an excess (6–fold) of sβ–CD in D_2O. There was no change in the chemical shifts of pyrrole (δ 6.78 ppm, 2H, *s*; δ 6.23 ppm, 2H, *s*), indicating no evidence for the host–guest complexation between the anionic sβ–CD and pyrrole. It seems that the sulfonated anionic pendants prevent the inclusion of pyrrole. The redox properties of the PPy–sβ–CD film is shown in Fig. 1(b), where the polymer was cycled in a neutral 0.1 M Na_2SO_4 solution at 50 mV s^{-1}. The voltammogram represents the first cycle and shows a large broad reduction peak at approximately −0.55 V vs SCE. This corresponds to the reduction of the polymer and the ingress of Na^+ ions from the solution. On the reverse scan, an oxidation wave, centred at about −0.30 V vs SCE, is evident and represents the oxidation of the polymer and the egress of the Na^+. This wave is somewhat smaller than the reduction wave which indicates that the egress of Na^+ is more difficult that its ingress and during the reverse sweep at 50 mV s^{-1}, not all the incorporated Na^+ is released. This is consistent with the cation exchange properties of PPy–sβ–CD [21, 22] and shows that the polymer is suitable for the uptake and release of protonated DA.

The surface morphology of PPy–sβ–CD is shown in Fig. 2(a). The characteristic cauliflower and globular morphology is evident. In addition, the surface appears to be organised into long linear segments that range in width between 8 to 43 μm. For comparison purposes, the surface morphology of polypyrrole doped with chloride, PPy–Cl, is presented in Fig. 2(b). In this case, the organised linear segments are absent and the globular structures are more disordered. As the anionic cyclodextrins are the only dopants present in solution, the sulfonate groups on the rim of the cavity provide the charge compensation as the polymer is formed in the oxidised state at the platinum substrate. The alignment of these negatively charged sulfonates at the positively charged polypyrrole backbone may be somewhat difficult given the size of the cyclodextrins and the number of adjacent anionic groups on the rim of the cavity, giving this somewhat different surface morphology.

Uptake and release of DA

The suitability of the PPy–sβ–CD system in the release of dopamine was investigated by varying the dopant in the polymer system. Polypyrrole films were prepared using 0.2 M pyrrole and 0.1 M concentrations of various dopants at 0.80 V vs SCE to a charge of 3 C, however the sβ–CD concentration was maintained at 0.01 M, as higher concentrations increased the viscosity of the solution. The incorporation of the DA was accomplished by applying a reduction potential of −0.90 V vs SCE in the presence of 0.10 M DA in a 0.1 M Na_2SO_4 solution, while the DA was released at 0.10 V vs SCE. The UV–visible spectra, recorded for the release of DA after a release period of 40 min for four different polymer systems, are shown in Fig. 3(a), while the absorbance at 280 nm plotted as a function of time is shown in Fig. 3(b). It is evident that the release of DA from the PPy–sβ–CD system is considerably higher. There is a two–fold increase in the release of DA on comparing PPy–PTS and PPy–sβ–CD, while the sulfate–doped polymer shows a much lower release rate, over the 30–min period, Fig. 3(b). Clearly, there is negligible release of DA with the smaller dopants which exhibit anion exchange. Although PTS (para–toluene sulfonic acid) is a large and immobile dopant, it is much less efficient in the release of DA. Furthermore, the UV–visible spectrum recorded for the DA released from PPy–PTS, Fig. 3(a), shows

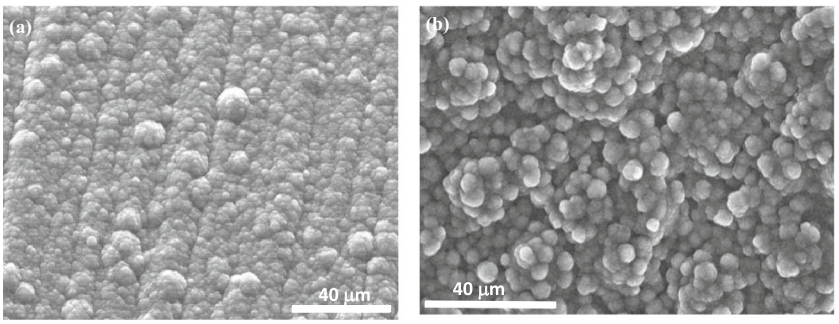

Fig. 2 **a** SEM micrograph of PPy–sβ–CD formed to a charge of 2.0 C and **b** SEM micrograph of PPy–Cl formed to a charge of 2.0 C

evidence of degradation. This is not surprising as DA is easily oxidised and has poor stability in solution in the presence of trace amounts of oxygen and on exposure to light. However, there is no evidence of any dopamine degradation on release from the PPy–sβ–CD system, which indicates that the Sβ–CD stabilises and protects the DA molecule.

The incorporation of DA at the PPy–sβ–CD system was studied by varying the applied potential employed in reduction of the polymer film, the reduction period and the influence of the supporting electrolyte. While the use of a supporting electrolyte will give rise to the presence of cations that will compete with the incorporation of the protonated DA, the supporting electrolyte will provide a more conducting solution. The influence of different concentrations of Na_2SO_4 on the subsequent release of DA at 0.10 V vs SCE, where the DA was incorporated at −0.80 V for 30 min is shown in Fig. 4. These data are consistent with increasing competition between the DA and the Na^+ as the supporting electrolyte concentration is increased. However, these increasing concentrations give rise to increasing conductivity and more efficient reduction of the polymer film. These opposing effects result in more efficient uptake of DA in a 0.10 M Na_2SO_4 solution. The EDX spectrum shown in the inset was recorded following the reduction of PPy–sβ–CD in 0.1 M Na_2SO_4 and 0.1 M DA and clearly shows the uptake of Na^+. While higher concentrations of DA are released during uptake in the 0.1 M Na_2SO_4, these competing reactions can be easily eliminated by removing the Na_2SO_4.

The influence of the applied potential employed in the uptake of DA is shown in Fig. 5(a). There is a near two–fold increase in the release of DA on varying the reduction potential from −0.40 V to −0.50 V vs SCE and then a more gradual increase in the DA levels is evident on increasing the potential to −0.80 V vs SCE. These findings are in good agreement with the redox properties of PPy–sβ–CD films, Fig. 1(b), where reduction of the polymer occurs on the application of potentials in the vicinity of −0.40 V to −0.70 V vs SCE. However, with potentials lower than −0.80 V vs SCE there is less efficient uptake of dopamine. This may be connected with the competing reduction of hydrogen ions at the platinum substrate. This competing reaction consumes the charge leading to less efficient reduction of the polymer. Furthermore, at potentials of −1.0 V vs SCE degradation of the dopamine was observed. Again, this was attributed to the hydrogen evolution reaction at the platinum–polymer interface, which occurs at potentials in the vicinity of −0.90 V to −1.0 V vs SCE at the neutral pH values used in these experiments. As this reaction occurs, an alkaline environment is generated giving rise to the decomposition of DA. Although the presence of the polymer will inhibit this reduction reaction, the polymer reduction periods of 30 min and higher are sufficient to generate a local alkaline environment. Indeed, some decomposition of the dopamine was evident at −0.90 V vs SCE when thicker polymer

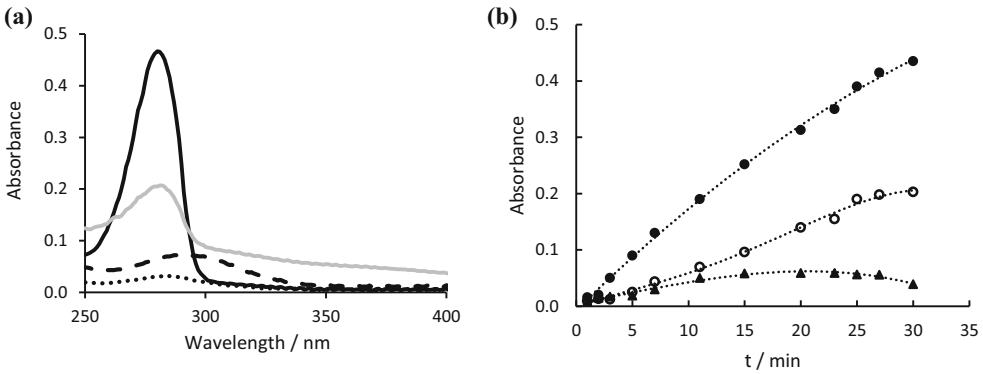

Fig. 3 **a** UV data for the release of DA at 0.10 V vs SCE after a 40–min release period from polymers prepared to the same final charge with (• • • • • •) NaCl, (— — —) Na_2SO_4, (——) PTS and (——) sβ–CD, **b** Absorbance plotted as a function of time for the release of DA from ● PPy–sβ–CD, ○ PPy–PTS and ▲ PPy–SO_4

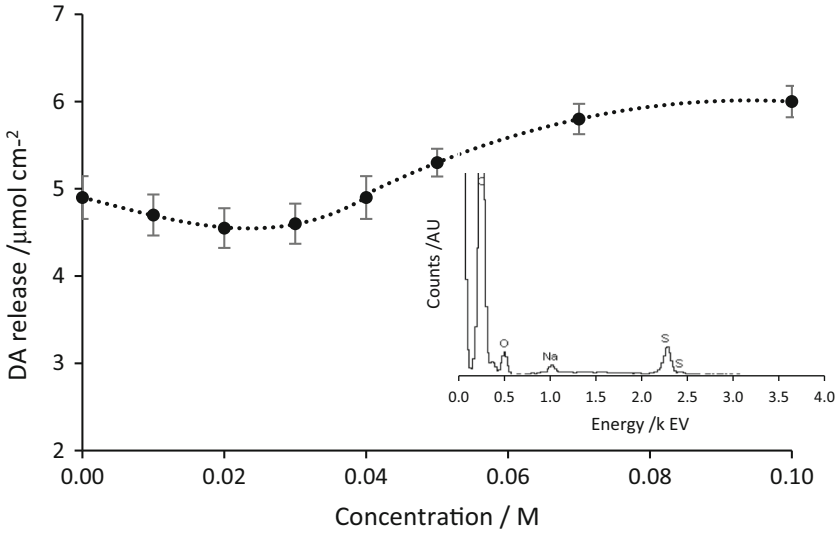

Fig. 4 DA release as a function of the Na_2SO_4 concentration used in the DA incorporation step at −0.80 V vs SCE for 30 min for PPy–sβ–CD films grown to 3.0 C, where DA was released upon application of 0.10 V vs SCE for 60 min ($n = 3$). Inset shows the EDX spectrum recorded following the reduction of PPy–sβ–CD at −0.80 V vs SCE in 0.1 M DA and 0.1 M Na_2SO_4

films were used and this is probably connected to the slower diffusion of hydroxide anions from the platinum interface and the buildup of a sufficient alkaline solution to decompose the dopamine. The influence of the reduction period is illustrated further in Fig. 5(b), where the charge consumed during reduction of the polymer at −0.80 V vs SCE is plotted as a function of the amount of DA released. The reduction charge of 1.5 C corresponds with a 60–min reduction period. This plot shows that there is a direct relationship between the DA levels released and the extent of polymer reduction during the uptake of DA, which controls the amount of DA incorporated.

The stimulated release of dopamine on the application of an oxidation potential of 0.10 V vs SCE is compared to the release observed in the absence of electrochemical stimulation in Fig. 6. The DA was incorporated at −0.80 V vs SCE for 30 min. It is evident that the amount of DA released, when a potential of 0.10 V vs SCE is applied, is considerably higher; almost a 15–fold increase compared to the data obtained under open–circuit conditions. The open–circuit potential was recorded during the release and this potential is plotted as a function of time and shown in the inset of Fig. 6. As the polymer was reduced at −0.80 V vs SCE, the potential increases slowly from this initial point and reaches a value of about −0.20 V vs SCE after 60 min. At these lower potentials, the polymer remains largely reduced and the dopamine is only released at a very slow rate. At 0.10 V vs SCE, the polymer is slowly oxidised and the dopamine is released in order to maintain charge balance. The release at higher potentials gave rise to much higher release rates, however the electrochemical oxidation of DA was observed at 0.25 V vs SCE.

Having selected an appropriate incorporation potential (−0.80 V vs SCE) and time (30 min) and a suitable release potential (0.10 V vs SCE), the polymer films were formed to different charges. These results are summarised in Fig. 7. A near linear relationship between the DA released and the electropolymerisation charge is observed for charges up to approximately 7 C, giving high release levels of 12 µmol cm^{-2} over a 60–min period. Higher release rates can be obtained with thicker polymer films reaching values of 14 µmol cm^{-2} for a polymer formed to 12 C.

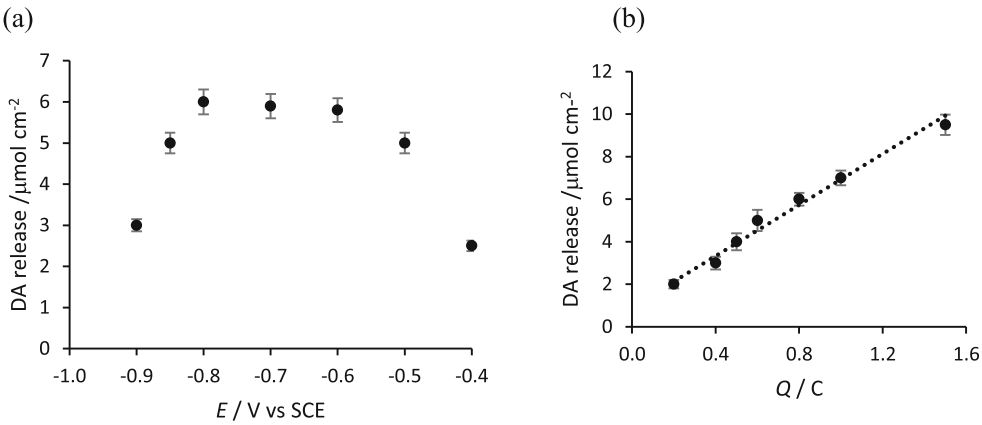

Fig. 5 DA release as a function of the **a** potential applied for 30 min and **b** charge consumed during the reduction of the polymer in the presence of 0.1 M DA in 0.1 M Na_2SO_4. DA was released at 0.10 V vs SCE for 60 min (n = 3)

Discussion

It is clear from the data presented that dopamine can be incorporated and released from PPy–sβ–CD. These events are summarised in Eq. 1, which describes the uptake of DA when the polymer is reduced, and Eq. 2, which represents the release of DA on the application of a more positive potential.

$$PPy^{n+}\text{–}(n/m)s\beta\text{–}CD^{m-} + ze^- + nDA^+ \rightarrow PPy^o\text{–}(n/m)s\beta\text{–}CD^{m-}nDA^+ \quad (1)$$

$$PPy^o\text{–}(n/m)s\beta\text{–}CD^{m-}nDA^+ - ze^- \rightarrow PPy^{n+}\text{–}(n/m)s\beta\text{–}CD^{m-} + nDA^+ \quad (2)$$

As shown in Fig. 4, the anionic cyclodextrin also attracts and uptakes sodium cations in the DA–containing solution. These will be maintained within the polymer matrix by electrostatic interactions between the anionic pendants and the hydrated sodium cation. However, it is evident that the Na^+ cations have a relatively small influence on the amount of DA incorporated. In the absence of the supporting electrolyte, approximately 5 μmol cm^{-2} DA are released and this amount is reduced only slightly as the sodium concentration is increased. This may indicate that the PPy–sβ–CD has some selectivity in relation to the uptake of DA and this can be explained by the formation of an inclusion complex between DA and the CD. The formation of this inclusion complex is facilitated by the electrostatic interactions between the protonated amine group of DA and the anionic pendants of the CD, while the more hydrophobic aromatic ring structure fits into the cavity of the cyclodextrins [40, 41]. It is also clear from Fig. 4 that the uptake of DA can be easily achieved in the absence of a supporting electrolyte and this would avoid the binding and release of Na^+.

The release rates achieved compare very well with previous publications that have employed conducting polymers. For example, Konturri et al. [42] demonstrated the release of 130 nmol cm^{-2} of salicylate, while Zinger and Miller [43] observed the release of 27 nmol cm^{-2} glutamate and Pyo et al. [44] obtained ATP release rates of 65 nmol cm^{-2} from polypyrrole films. To the best of our knowledge the only other paper reporting the release of DA, using polypyrrole films, was published by Miller et al. [6]. In this study, the release of DA from polypyrrole films grown galvanostatically to a charge of 0.6 C was reported as 110 nmol cm^{-2}. Although the polymer films employed in this study were deposited to higher charges, the data in Fig. 7 can be used to estimate the release at 0.6 C to give approximately 1.86 μmol cm^{-2} giving a 16–fold increase with the PPy–sβ–CD film, while more significant levels of 6.0 μmol cm^{-2} can be obtained with thicker polymer films deposited to 3.0 C.

It is clear from these comparisons and Fig. 3 that the PPy–sβ–CD system releases higher rates compared to other polypyrrole systems. This is probably related to the 7–11 sulfonated groups attached to the cavity of the CD which facilitate the uptake of the protonated DA. Another important consideration is the number of sulfonated groups on each cyclodextrin that takes part in the doping process. If all the sulfonated groups were involved in charge balance this would not only place strain on the CD but also lead to considerable steric hindrance

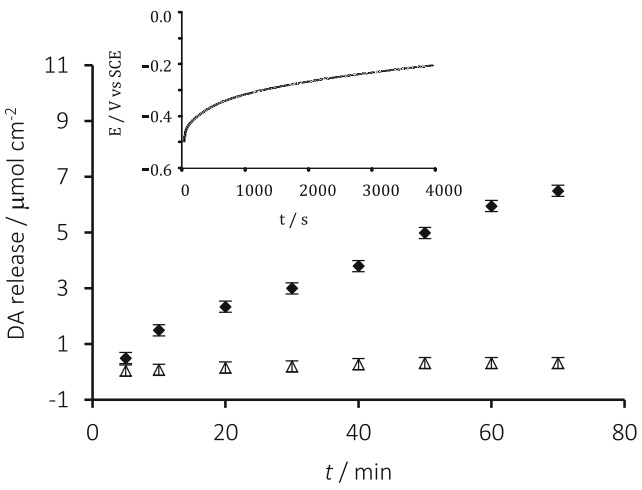

Fig. 6 DA release as a function of time for polymers stimulated at ♦ 0.10 V vs SCE and Δ under open–circuit conditions (n = 3) where the DA was incorporated at −0.80 V vs SCE for 30 min, inset shows the variations of the open–circuit potential during release

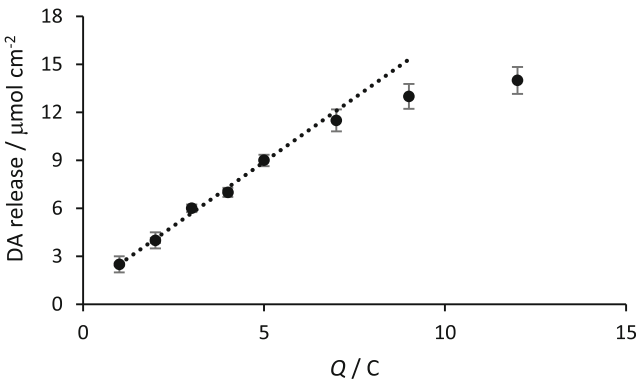

Fig. 7 DA release from the polymers formed at 0.80 V vs SCE to various charges in the presence of 0.20 M pyrrole and 0.01 M sβ–CD where DA was incorporated and released upon application of −0.80 V for 30 min and 0.10 V vs SCE for 60 min, respectively

in the polymer matrix. It is probable that some free sulfonated groups are present. Indeed, Naoi and co–workers [45], in studying the doping of polypyrrole with sulfonated naphthalene, concluded that the polypyrrole–trisulfonate doped films possessed free sulfonated groups without any charge compensation. These free sulfonate groups will also attract the protonated DA. As detailed earlier, L–DOPA is currently used in the management of Parkinson's disease. It was also possible to uptake and release this molecule using PPy–sβ–CD, however more acidic conditions were required for its uptake. This molecule is a zwitterion, where the amine group is protonated and the carboxylic group is dissociated. As the p*K*a of the carboxylic group is 2.32, then the protonated L–DOPA will exist at pH values lower than 2.32 and it was at these pH values that efficient uptake of L–DOPA was observed. Again, this illustrates the prominent role of the electrostatic interactions.

In addition to providing high release rates, the PPy–sβ–CD system appears to protect the DA molecule as shown in Fig. 3(a). While the sβ–CD provides a high charge facilitating a strong electrostatic interaction with the protonated DA, an inclusion complex can also be formed [40, 41]. This inclusion complex, where the DA molecule is included in the cavity, appears to protect the molecule from oxidation and degradation. When the PPy–sβ–CD is oxidised, the positively charged backbone will exert repulsive forces on the included DA and these seem to be sufficiently strong to release DA from the cavity. While many of the recent publications [8–18] have focused on increasing the polymer surface area to give higher release rates, these results show that the nature of the dopant is equally important. Furthermore, the applied release potentials used in this study are very low at 0.10 V vs SCE and these can be easily reached without the application of an external potential.

Conclusion

The performance of polypyrrole doped with two small anions and two large anions, PTS and sβ–CD, in the uptake and release of DA, showed that the sβ–CD dopant facilitated the incorporation and release of significantly higher concentrations of DA. These effects were attributed to the large size of the sβ–CD dopant with 7–11 sulfonated groups on the rim of the CD cavity, which provides an immobile dopant with a large negative charge that is capable of binding large amounts of DA on reduction of the polymer. In addition, the DA forms an inclusion complex with the sβ–CD and this enables higher uptake of DA and this inclusion complex seems to stabilise the DA molecule. This analysis can also be extended to the release of L–DOPAC, the DA precursor employed in the management of Parkinson's disease.

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