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A detailed insight into drug delivery from PEDOT based on analytical methods: Effects and side effects

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Abstract: The possibility to release drugs from conducting polymers, like polypyrrole or poly(3,4-ethylenedioxythiophene) (PEDOT), has been described and investigated for a variety of different substances during the last years, showing a wide interest in these release systems. A point that has not been looked at so far however is the possibility of other substances, next to the intended ones, leaving the polymer film under the high voltage excursions during redox sweeping. In this study we target this weakness of commonly used detection methods by implementing a high precision analytical method (high-performance liquid chromatography) that allows a separation and subsequently a detailed quantification of all possible release products. We could identify a significantly more complex release behavior for a PEDOT:Dex system than has been assumed so far, revealing the active release of the monomer upon redox activation. The released EDOT could thereby be shown to result from the bulk material, causing a considerable loss of polymer (>10% during six release events) that could partly account for the observed degradation or delamination effects of drug-eluting coatings. The monomer leakage was found to be substantially higher for a PEDOT:Dex film compared to a PEDOT:PSS sample. This finding indicates an overestimation of drug release if side products are mistaken for the actual drug mass. Moreover the full picture of released substances implements the need for further studies to reduce the monomer leakage and identify possible adverse effects, especially in the perspective of releasing an anti-inflammatory substance for attenuation of the foreign body reaction toward implanted electrodes. J Biomed Mater Res Part A: 103A: 1200–1207, 2015.

Key Words: PEDOT, neural electrodes, drug release, dexamethasone, HPLC, electrochemical release

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INTRODUCTION

Electrochemically controlled release from conducting polymer based systems has gained substantial interest, especially within the field of neural engineering.[1] The proposed mechanism thereby is that drugs, incorporated in the polymer during synthesis, are released by electrostatical forces, supported by a mechanical actuation due to interaction of the polymer with the surrounding electrolyte during redox cycling.[2–5] Such redox triggered release has been shown for a variety of biologically relevant molecules, for example Dex, nerve growth factor, brain-derived neurotrophic factor, adenosine 5′-triphosphate, risperidone and progesterone[2,4–13] and results show that release is influenced by the current passed over the interface upon redox cycling as well as conformational changes in the film associated with the electrochemical processes. A detailed description of multiple polymer based release systems can be found in the excellent reviews of Svirskis et al.[14] and Pillay et al.[15] What is however not accounted for in most of the previous studies is the possibility of other substances leaving the polymer film as a result of the extensive voltage excursion. The main methods used to quantify release are ultraviolet (UV) absorption spectroscopy,[2–5,9,10] electrochemical quartz crystal microbalance (EQCM),[4,16] enzyme-linked immunosorbent assays (ELISA),[17] and radiometric measurements[18] (see Table I). Unfortunately, all of these methods have limitations when it comes to providing the full picture of what is released from the system.

UV absorption has been successfully proven for the detection of Dex, with a linear correlation between absorbance of solution at 245 nm wavelength and concentration of Dex down to 0.5 μg/mL. However, the method does not discriminate between Dex and other UV active substances that could possibly be in the solution. EQCM is a

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TABLE I. Limitations of Commonly Used Release Quantification Methods

	UV Absorption	EQCM	ELISA	Radio Labeling
Selective quantification of target substance	No	No	Yes	Yes
Detection of byproducts	No	No	No	No
Expected consequence	Incorrect release information by overestimation	Incorrect release information by overestimation	Incomplete release information	Incomplete release information

highly precise method for quantifying mass changes in the electrode film. The method is not selective but only presents the summed up mass for substances leaving the electrode which in principle can be anything from complete polymer fragments to ions of the supporting electrolyte. Furthermore, alterations of viscoelastic properties of the film upon redox cycling might add to changes in the frequency as observed by Efimov et al.[19] which could further impair the measurement. Using ELISA and radiometric labeling makes it possible to truly single out the release of the intended molecule from any background signal in the solution. On the other hand, also these methods overlook the possibility of by-products leaving the polymer as a result of stimulation.

Most studies use a rather broad cyclic voltammetry sweep range, that is −0.8 V to 1.4 V[2,3], to drive the intended drugs into solution. It is not unlikely that other molecules, apart from the target substance, could be expelled as a consequence of this activation. None of the aforementioned methods would account for such an event and would thereby lead to misinterpretation of results.

To give a more complete picture of the eluted substances from a conducting polymer film, this study addresses the analysis of release samples using two different quantification techniques, high-performance liquid chromatography (HPLC) and EQCM. Due to recent interest in poly(3,4-ethylenedioxythiophene) (PEDOT) films for drug release,[3,10] replacing the lastly more popular polypyrrole (PPy), electropolymerized PEDOT:Dex was chosen as drug delivery system for this study. An HPLC protocol was established to allow the quantification of Dex and further UV active substances at concentrations below 5 ng/mL. This method, in contrast to pure UV absorption, first induces a separation of the sample into its different chemical constituents, which can be identified by the time they need to pass through the analytical column. Signals from different UV active substances, which in the absence of a separation step would have been summed up by the detector, can with the HPLC be distinguished as separate peaks over time. With the given method we could see that the release signal in fact was determined by three different substances which could be identified as Dex, salt ions from the supporting electrolyte and the monomer EDOT. As furthermore the summation of the different substances did not account for the full mass as detected by the EQCM method, parametric studies were performed to unravel a more complex release mechanism.

MATERIALS AND METHODS

PEDOT:Dex deposition

Polymer films for release analysis were electropolymerized from an aqueous solution containing EDOT and Dex (dexamethasone 21-phosphate disodium salt; purchased from Sigma and used without further purification) at a concentration of 0.01 *M* each, which was found efficient for the monomer[20] and the counterion[21] concentration in previous studies. The solution was mixed intensively on a vortex and additionally sonicated (30 min at 135 W) for homogenization before use. Polymer deposition was conducted in a conventional three electrode setup using a potentiostat (Autolab128N, Metrohm) in galvanostatic mode (80 μA/cm^2) for realization of homogeneous and well adhering coatings. Layer thickness was determined by the charge transferred during the polymerization and set to 100 mC/cm^2 for the screen printed Pt-electrodes (SPE, Dropsens, 4 mm diameter) as well as the platinized EQCM electrodes (6 mm diameter), which were connected as working electrodes. Samples were carefully rinsed with MilliQ-water (30 s exposed to a water jet, using a volume of 30 mL) after fabrication as well as between each release experiment and stored in separate containers, filled with 1 mL of electrolyte [phosphate-buffered saline (PBS)].

Release triggering

Release of Dex was triggered by CV-sweeping the film in PBS in the range of −0.6 V to 0.9 V versus Ag/AgCl except for the parametric study where the range is split into a cathodic sweep (−0.6 V to 0 V) and the corresponding anodic sweep (0–0.9 V). One release set covers five subsequent sweeps at a speed of 0.1 V/s. CV-sweeps were performed in this broad range to ensure maximum release efficiency and were further confined by the electrochemically safe limits associated with the water window for platinum in saline solution. The passive storage time in PBS between the single actuations was kept at 96 h unless otherwise specified.

Release quantification

The quantification was performed on a waters 2695 separation module (HPLC) with a C18 column and a UV detector (Agilent 1260 infinity series) which was operated at a wavelength of 245 nm. The mobile phase was based on the work of Iqbal et al.[22] and purged at a flow-rate of 0.5 mL/min at room-temperature through the column. A composition of 25.7% methanol, 29.8% acetonitrile and

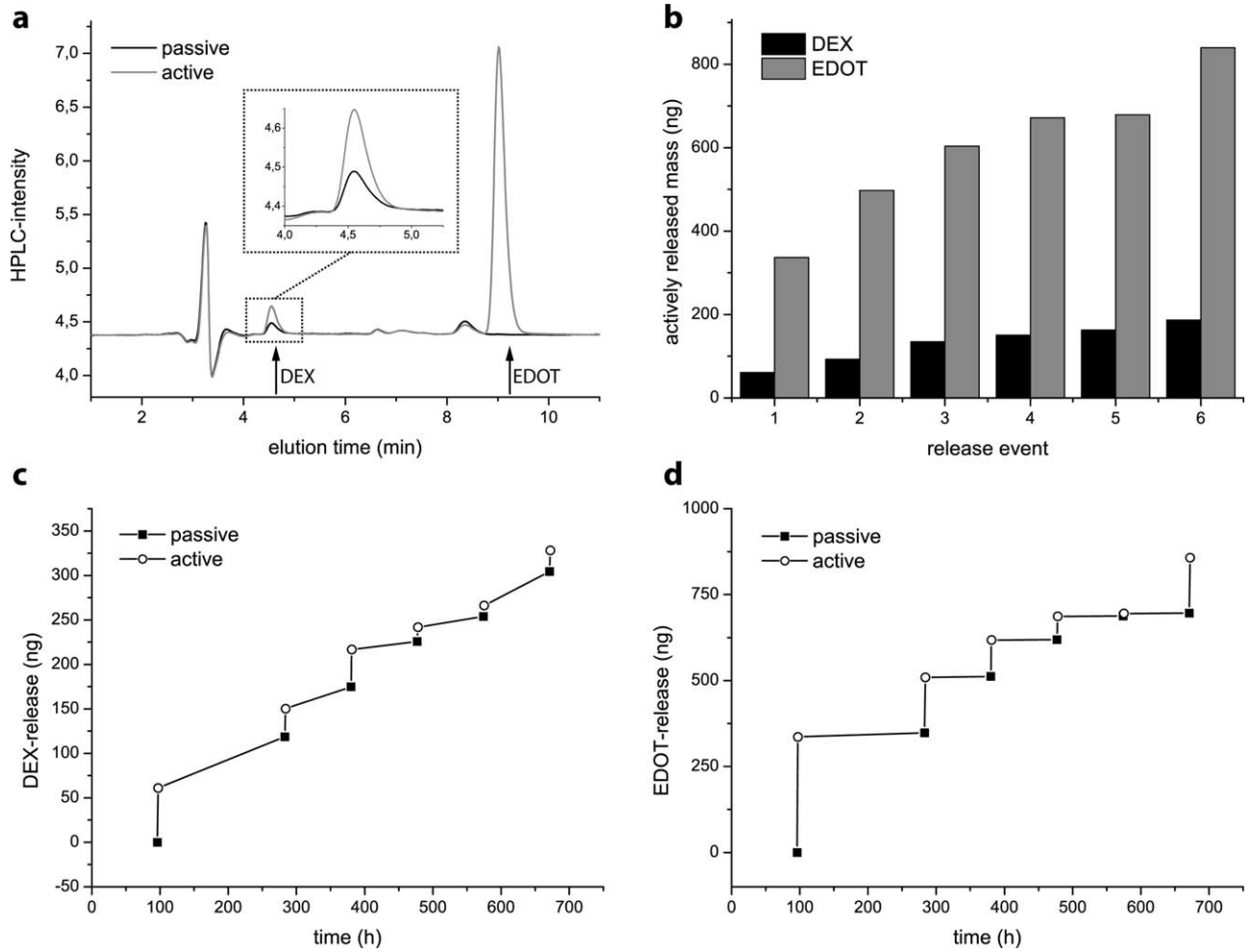

FIGURE 1. Full picture of released substances unraveled by analytic chromatography. (a) HPLC-peak histogram showing the presence of EDOT in the release solution. (b) Mass comparison for actively released Dex versus EDOT showing a significant EDOT signal. (c) Cumulative true Dex release over time and (d) cumulative EDOT release upon redox activation of a PEDOT:Dex film.

44.5% buffer solution was accordingly used with a 0.048 M NaH_2PO_4 buffer, adjusted to a pH value of 5.4 using a KOH solution. A sample volume of 100 μL was injected to the column and the peak separation was observed over a time of 15 min which covered all detectable peaks. Retention times were identified using separate injections of either PBS, Dex, or EDOT at different concentrations, which simultaneously formed the data basis for the calibration curves. Mass calculation was done by peak integration and lead to successful quantification with a limit of detection (LOD) of 0.4 ng/mL and a limit of quantification (LOQ) of 1.3 ng/mL for Dex and, respectively, 0.9 ng/mL and 3.1 ng/mL for the EDOT monomer. Calibration curves were linear between 0.01 μg/mL and 4 μg/mL with an R^2 of 0.99931.

EQCM measurements were performed with an Autolab potentiostat using a platinized TiO_2 crystal (Metrohm) with an oscillation frequency of 6 MHz. Mass calculation was done according to the Sauerbrey equation $\Delta f = \Delta m \times C_f$, adopting a sensitivity constant (C_f) of 0.0815 ng/Hz cm^{-2} for the used crystals. Minimum resolution was determined by a frequency change of 10 Hz, corresponding to a mass change of 35 ng.

RESULTS

HPLC-based release analysis

Electropolymerized PEDOT:Dex films with a coating-thickness of 700 nm and a total polymer mass of nearly 16 μg (for a deposition charge of 100 mC/cm^2) were subjected to redox-triggered drug release over a time period of one month using PBS as release medium. The detailed analytical investigation of the release solution in the HPLC revealed that the signal was mainly determined by three different species [Fig. 1(a)]. The first one appearing around 3 min elution time is assigned to the ions in the release buffer itself and shows some minor differences between passive and active samples caused by the ion-exchange with the polymer upon redox activation. The second peak with an elution time of 4.6 min corresponds to Dex and shows variations in intensity, depending on the amount of released drug under passive and active conditions. Next to these expected peaks, there is however an additional peak (elution time of 9

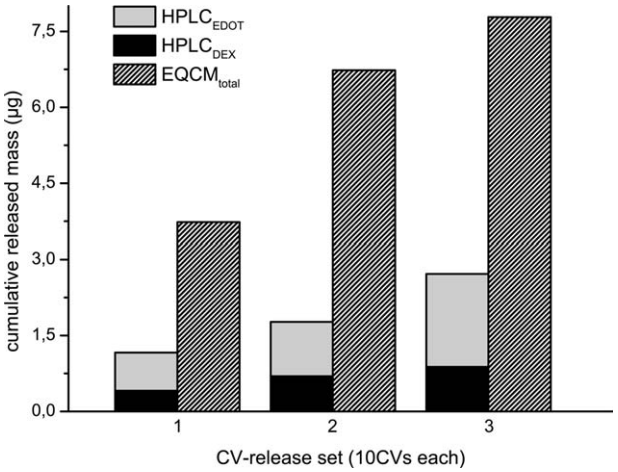

FIGURE 2. Release quantification comparison using HPLC and EQCM methods proves a significant overestimation of drug-release if the full range of expelled substances is not considered. Next to the actual drug expulsion, the release of EDOT as well as the possible loss of complete polymer fragments needs to be considered for true drug-level estimations. The figure shows data obtained for $n = 1$.

min) with substantial contribution to the signal. By running corresponding calibration and reference samples containing either Dex or EDOT in a PBS buffer, this could be identified to result from the monomer EDOT. The monomer associated peak also displayed a significant difference between the passive and the active release solution which clearly indicates an active release characteristic similar to what could be identified for the drug. This behavior can be seen in the cumulative release curves displayed separately for Dex [Fig. 1(c)] and the monomer [Fig. 1(d)] where the actively triggered release and the slower passive leakage between the actual release measurements are shown over time. It is worth mentioning, that a single active release event is performed within a timeframe of 15 min whereas the passive storage time is almost 400 times longer. Plotting the actively released mass for Dex and EDOT next to each other [Fig. 1(b)], one can clearly see a substantially higher mass coming from the monomer compared to the targeted drug. The small peaks between 6 min and 9 min elution time [Fig. 1(a)] could not be correlated to any specific substance but were found to be part of the background of the PBS solution, either originating from the buffer itself or resulting from elution products from the storage vials. Since interference with the target peaks (Dex and EDOT) could be excluded, these peaks were not further considered in the detailed analysis.

Mass determination using EQCM and HPLC

A comparison of the mass determination based on the EQCM technique versus the HPLC measurement is shown in Figure 2 for a PEDOT:Dex film deposited with 100 mC/cm^2 charge density. The release triggering is performed in the range of −0.6 V to 0.9 V with 10 CV-sweeps comprising one release event for this sample to ensure a significant mass change on the EQCM. The cumulative data displays a clear difference between the two mass measurements, performed on one and the same sample with two different and independent (noninterfering) techniques. Thereby not only an overestimation due to the nonobservance of EDOT is apparent, as has been predicted from the previous results, but additionally the EQCM measurement shows significantly higher release values with a difference of more than factor two.

Influence of the polymer:dopant system on the EDOT release

A comparison of a PEDOT:Dex coating with a PEDOT:PSS film, deposited under equal conditions, is provided in Figure 3(a) with focus on the EDOT-release. Albeit both sample types show an actively triggered release of the monomer a clear difference between the two films is apparent, indicating a weaker polymer structure for the drug loaded film. The coating with the Dex counterion lost a substantial amount of EDOT during five activation steps while the sample having the PSS counterion mainly lost some monomer during the first activation, followed by a subsequent insignificant expulsion at levels close to the detection limit.

Sweeping the PEDOT:PSS film after initial stabilization of the monomer leakage for 250 CV scans however results in an expulsion of 68 ng of EDOT (62 ng for another 250 scans) which demonstrates that also the more stable polymer:dopant configuration is subject to a redox driven monomer loss even though the absolute loss (1% over 250 CVs) is significantly lower compared to the PEDOT:Dex films (10% over 6 CVs).

As expected, there was no Dex peak visible in the PEDOT:PSS sample while the EDOT peak clearly remained (spectrum not shown). This supports that the second peak is truly attributed to the monomer EDOT and not an oxidation or reduction product of the Dex due to the applied stimulation. A further confirmation that the peak can be assigned to EDOT is additionally given by the data in Figure 3(b), where a PPy:Dex film (fabricated equally to the PEDOT:Dex equivalent) was analyzed, showing an overlap of the Dex and the Py-monomer peak at 4.4 min but lacking any signal at 9 min, which would correspond to the elution time for the EDOT-monomer. The quantification of the influence from possible Py-release during redox activation could not be done with the present HPLC-method as the partitioning conditions do not separate this peak sufficiently from the others.

Redox and interface dependency of EDOT release

A parametric study was conducted to further identify the origin and the redox-dependency of the EDOT in the release solution. Therefore, PEDOT:Dex samples were subjected to separated redox sweeps according to Figure 4(a,b) with either a cathodic sweep from −0.6 V to 0 V or an anodic sweep from 0 V to 0.9 V. Results show a clear release of the anionic drug during the cathodic sweep, however, there is also a distinct release of Dex for the sample only experiencing the anodic sweep. The total amount of released substances is generally lower for the anodic sweep range even so the transferred charge in the anodic sweep was 1.6 times higher compared to the cathodic one. Overall, the release of

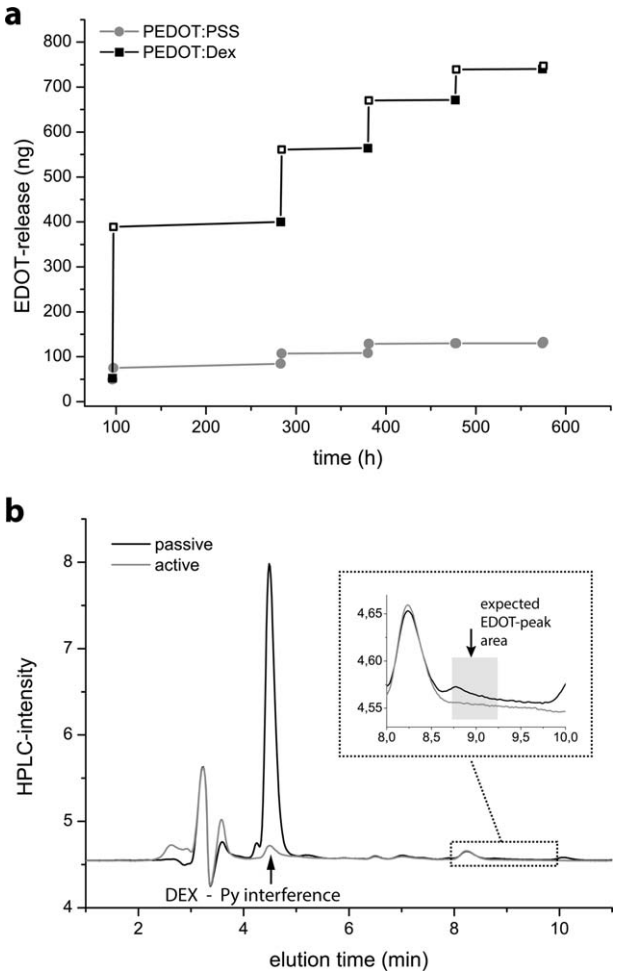

FIGURE 3. EDOT release from different polymer systems. (a) Cumulative release of EDOT from a PEDOT:Dex film in comparison to a PEDOT:PSS film showing the higher monomer loss on the drug-loaded sample due to lower polymerization/doping efficiency as for the PEDOT:PSS. (b) HPLC analysis of a PPy:Dex reference sample does not show any peak at an elution time of 9 min which proves the correlation of this peak to EDOT. A Py-monomer peak is not visible due to overlap with the Dex and PBS peaks between 2 min and 5 min. The peak at 8.2 min in the inset is attributed to the salts in the solution and the tiny peak in the passive solution at 8.7 min results from elution products of the plastic vial during passive storage, having a different peak center than the EDOT-monomer. The figure shows data obtained for $n = 1$.

Dex and EDOT is affected by the full sweep potential showing a higher efficiency of the Dex:EDOT release ratio in the anodic area for activation #1 and #2 (with 5 CV sweeps per activation). Increasing the amount of redox cycles by factor 2 (10 CV sweeps per activation) for release events #3 and #4 leads to equalization in the Dex:EDOT ratio between anodic and cathodic sweeps. However, there is no clear suppression on either the positive or the negative range for actively releasing EDOT from the coating.

Figure 4(c,d) shows the second parametric study where a composite layer was used to identify whether the EDOT release is associated with the interface to the substrate or rather originates from the polymer bulk. Sample A consists of a thin PEDOT:PSS layer (10% of the film) in contact to the substrate with a PEDOT:Dex layer (90% film thickness) on top, while sample B has the reversed layer composition. Release for Dex [Fig. 4(a)] showed as expected high mass values for sample A with the thick PEDOT:Dex layer. Sample B, featuring a capping layer of PEDOT:PSS on top of the drug-film, surprisingly also showed Dex release upon redox activation, even so less drug was released in comparison to sample A. More interestingly however, the release of EDOT is basically only present for sample A if neglecting the initial minor release at sample B. This finding demonstrates that the monomer leakage results from the polymer bulk rather than the interfacial layer and hence is not attributed to a failure at the interface to the substrate. At this point it should be mentioned, that the samples were carefully rinsed between all measurements so that no loosely attached EDOT was left on the surface. The generally very low passive release over 96 h compared to the significantly increased release within 15 min of actuation supports that the monomer leakage does not result from loose EDOT but is truly a consequence of redox sweeping.

DISCUSSION

Toward a more comprehensive understanding of the species released upon electrical stimulation

Conducting polymer coatings have often been suggested to enable the release of biologically relevant substances on demand upon applying an electrical trigger signal. Thereby various methods have been applied to quantify the amount of released molecules in solution, for example, UV absorption, EQCM and ELISA. However, these methods have limitations, with a substantial problem being that they fail to detect if additional species are released from the film apart from the intended ones.

Using highly precise chromatographic measurement methods (HPLC), we were able to identify a significantly more complex release behavior for a PEDOT:Dex system than has commonly been assumed so far. The most important finding, that the monomer EDOT is released next to the Dex, has impact on the current understanding of electrochemically triggered release from PEDOT films. As the monomer is UV active at the same wavelength than the Dex (245 nm), release measurements neglecting the separation of released substances might be affected by a significant overestimation of release.[3,10] Based on these findings we believe that similar effects might influence also the formerly more popular PPy:drug[2] systems, and data indicating this has already been shown in the work of Svirskis et al.[11] In their studies they target risperidone release upon electrical activation of a Polylpyrrole:drug film, but next to the drug, also a monomer signal could be identified in the release solution, revealing an expulsion of Pyrrole.[11,12] Even so this finding was not further analyzed regarding an actively triggered expulsion, it supports the herein proposed theory that monomers can leave the polymer film upon redox activation.

The comparison between a PEDOT:Dex and a PEDOT:PSS film, actuated and measured under equal conditions, showed that the PEDOT:PSS sample released significantly less monomer than the drug loaded film. This observation is

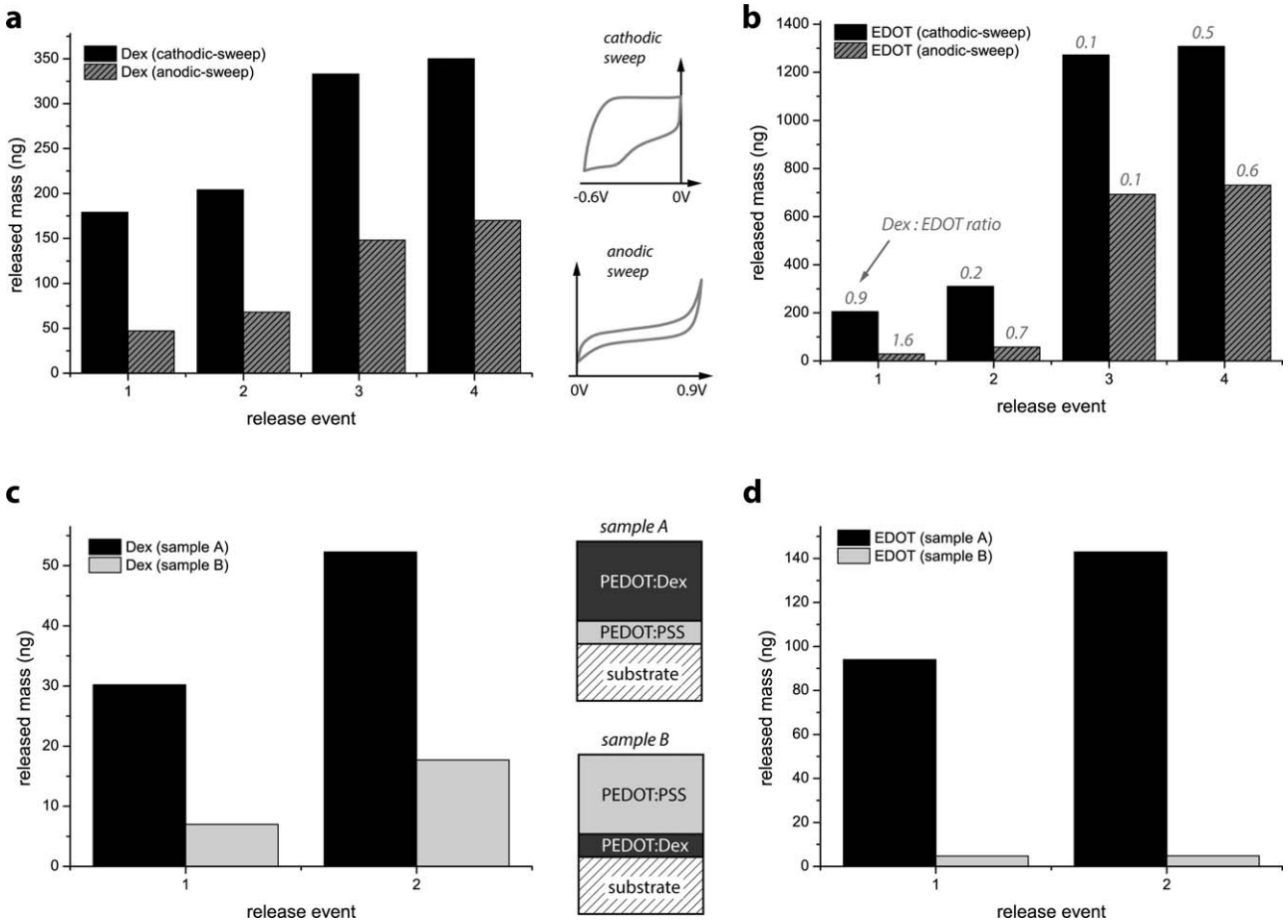

FIGURE 4. Parametric study of the EDOT release. (a) and (b) show the release of Dex and, respectively, EDOT under solely anodic or cathodic release conditions. The overall present release shows no clear correlation to a specific voltage range but implies that next to the electrostatical release mechanism also the swelling upon activation contributes significantly. The ratio of Dex versus EDOT release is additionally given as numerical values in the EDOT release graph. (c) and (d) show the release of Dex and EDOT for a stacked layer as shown in the center. Release data leads to the assumption that the monomer expulsion originates from the polymer bulk rather than the interface. The figure shows data obtained for $n = 1$ in each configuration.

in good agreement with the commonly reported higher polymerization/doping efficiency of the PEDOT:PSS system, resulting in a more stable polymer matrix. Due to the different behavior of the two polymer systems upon redox cycling (loss of dopant with partial replacement of electrolyte ions for PEDOT:Dex versus incorporation and expulsion of electrolyte ions at stable dopant level for PEDOT:PSS), the subsequent release of the dopant in form of the drug is further assumed to affect the polymer integrity. As the CV-sweeping parameters are equal for both film types we conclude that the potential excursions are not solely responsible for the EDOT loss during stimulation but the polymer-dopant interaction plays a substantial role. The generally weaker doping efficiency in combination with a loss or exchange of the dopant for a different species (electrolyte anions) accordingly leads to the significantly higher monomer loss of the PEDOT:Dex coating. However, there is nevertheless an active EDOT release for the PSS-sample, stressing the need for further investigations on the stability of conducting polymers under redox cycling.

New perspective on released masses

A comparison between the released masses from a PEDOT:Dex film, estimated using either an EQCM or the HPLC method, showed a difference of more than a factor two between the two methods. This demonstrated descriptively the effect of the previously described overestimation if released substances are summed up and misinterpreted for the actual drug mass as shown in Figure 2. It should be noted here, that alterations of the viscoelastic properties of the film upon redox cycling might additionally affect the mass calculation for the EQCM method relying on the Sauerbrey equation $\Delta f = \Delta m \times C_f$. The linear approximation between frequency change and mass does not take into account influences such as surface roughness and viscosity of the coating or the solution as described by Efimov et al.[19] However, based on the significant offset, we believe that this effect cannot entirely explain the observed results. The difference indicates that the release behavior from PEDOT:Dex films is rather complex and next to the EDOT release, also the ion-exchange with the supporting

electrolyte and a plausible release of complete polymer fragments play a role for the redox-based release. The expulsion of larger fragments cannot be seen in the HPLC due to the required prefiltering of the sample solution with a membrane of 0.45 μm pore size which excludes particles but does not affect the ionic drug and monomer molecules.

The calculation of the deposited mass for the polymer and its anion using the deposition charge Q_{dep} and the molecular mass M_x according to equation $m_{dep} = Q_{dep}F^{-1}(M_{EDOT} + \gamma M_{Dex})(2+\gamma)^{-1}$ with the Faraday constant F and doping level $\gamma = 0.3$[23] leads to a theoretically deposited mass of 16.8 μg for the 100 mC/cm^2 film. This number splits into 8 μg for the monomer and 8.8 μg for the drug which is close to the total mass of 15.4 μg that has been determined during the deposition with the EQCM. Comparing these values with the release data, it is apparent that a significant part of the monomer is lost during stimulation of the drug-loaded film [>10% within 6 actuations, Fig. 1(b)]. This loss of polymer substance is further assumed to lead to a progressing weakening of the polymer film itself. Consequently, this process is likely to contribute significantly to the manifold observations of delamination and/or degradation of polymer coatings from the substrate under redox based drug delivery.[2,3,24]

Redox and interface dependency

Parametric studies, performed to identify the correlation between actuation signal and released mass, showed higher drug and EDOT expulsion for the cathodic range (−0.6 V to 0 V). This is in good accordance with the expected electrostatical release mechanism reported by others.[2] However, there is also a considerable release of both Dex and EDOT in the anodic sweep, which indicates that not only the electrostatical mechanism but also the swelling and deswelling of the film during actuation contribute significantly to the drug release. Studies by Svirskis et al.[11,13] showed the successful release of cationic (risperidone) as well as neutral (progesterone) substances during electrical activation of a PPy film, which demonstrates the substantial effect of mechanical film actuation on the expulsion of charged and uncharged molecules. This mechanical release mechanism is further believed to dominate the active EDOT release from our samples as no clear suppression can be seen in any of the sweep ranges, which would be expected for a direct correlation to the sweeping potential. The EDOT loss was found to be generally lower in the anodic range, even so the transferred charge was 1.6 times higher than for the cathodic range. We hypothesize that a possible re-polymerization of monomers (or oligomers) under sufficiently high positive potentials, as provided in the anodic sweeps, leads to this observation.

The origin of EDOT molecules, leaving the polymer film upon redox activation, was assessed by investigating stacked layer samples as illustrated in Figure 4. Using these probes, we were able to identify that the monomer loss is mainly attributed to the polymer bulk and not determined by weak interfacial adhesion of the PEDOT to the substrate. An interesting finding here is that sample B (buried PEDOT:Dex layer) still features an active release of the drug even so the molecules have to pass all the way through the PEDOT:PSS before they reach the supporting electrolyte. This leads to the conclusion that redox release of the polymer does not only affect the top few nanometers of the coating but the complete polymer mass down to the substrate is involved. It is worthwhile mentioning that the PEDOT:PSS is not readily able to release the dopant anion in the same way as the PEDOT:Dex. In the latter case the top part of the polymer is assumed to be able to compensate the applied charge during release by expulsion of the anion so that no release from deeper structures is required, even so theoretically possible.

Although not shown in graphs, a broader set of samples was studied under similar conditions. Due to slight variations during the fabrication, samples do not acquire identical conductivity. Therefore, the potential driven release will also not induce identical current flow in each sample which makes a one to one comparison more difficult. It should be noted that release data was overall consistent with the representative samples shown in this report and no substantial deviations from the behavior described here could be seen in the larger sample set. Independent of the polymerization mechanism (galvanostatic vs. potentiostatic) or the film thickness, an active EDOT expulsion could consistently be identified for five additional samples (not shown here) whereas the ratio of released Dex:EDOT was found to vary between 1.02 and 2.44 (excluding the initial burst and depending on the actual sample configuration).

CONCLUSION

An analytical method could be successfully established to provide a deeper insight into the full release spectrum of substances leaving a PEDOT:Dex film upon redox activation. The separation of the single substances in the release solution thereby showed that next to the intended drug, also a significant portion of the monomer EDOT left the film. This EDOT release was found to be directly coupled to the redox activation. Furthermore the EDOT was found UV active at the same wavelength as the Dex (245 nm), which leads to a significant overestimation of drug release if separation would be disregarded like, for example, in the commonly used UV absorption technique. A comparison with the EQCM method confirmed this finding, displaying a difference of more than factor 5, which shows the relevance of implementing a proper release analysis for true quantification of released drug.

A parametric study, implementing different CV-ranges, unraveled that release triggering is not solely based on the elimination of the electrostatical binding of the dopant to the polymer. Moreover, the mechanical actuation of the polymer contributes significantly to the release of the drug and the monomer as has been described by others for different drugs.[2,3,5,11] The EDOT could be shown to originate from the polymer bulk. This substantial release of EDOT during redox is assumed to contribute to a progressive weakening of the polymer matrix. This consequently would lead to the delamination/degradation effects of conducting polymers

under release conditions, which has been often observed.[2,3,24] Interestingly, redox-triggered polymer degradation also affected the more stable PEDOT:PSS system which would have implications for the outcome of long-term cycling of the film. It could not be excluded that also PPy films release monomers. Such unintentional release of monomers might interfere with the target application (i.e., Dex release for anti-inflammatory treatment of tissue around implants) and counteract the benefit of releasing a drug in the first place. Therefore, future work should be invested into increasing the ratio of intentional versus unintentional release.

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