Tailorable drug capacity of dexamethasone-loaded conducting polymer matrix

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Abstract. The unique properties of conducting polymers, which are in the same time biocompatible and electrically responsive materials, make them perfect candidates for controlled drug release systems. In this study, the electrically-triggered controlled release system based on dexamethasone-loaded poly (3, 4-ethylenedioxyxpyrrole) (PEDOP) matrix is described. It is shown that the electropolymerization conditions can facilitate or suppress the formation of PEDOP/Dex matrix, as well as they can have the effect on its electrochemical performance. The release experiments performed in three different modes show that the drug capacity of PEDOP matrix increases with the increase in Dex concentration in the step of matrix synthesis, and higher Dex concentrations make it easier to control the amount of Dex released in an electrically-triggered mode. These results confirm the importance of the careful optimization of immobilization conditions to maximize drug capacity of matrix and maintain its electrochemical properties.

1. Introduction

Apart from their unquestionable success in organic electronics, conducting polymers have been recently discovered as robust and efficient materials for biomedical engineering [1,2]. The major advantage of this type of materials lies in the fact that together with proven biocompatibility [3]. They are able to change their physicochemical properties as the result of electrical stimulus [4]. Those unique properties make conducting polymer perfect candidates for the electrically-triggered controlled drug release systems. This has been already confirmed by numerous literature reports describing the immobilization and release of anti-inflammatory drugs [5], antibiotics [6] and anti-cancer agents [7,8].

Dexamethasone (Dex) is a highly potent glucocorticoid drug with a strong anti-inflammatory and immunosuppressant effect, known from its efficiency against cerebral edema. Therefore, it is frequently used to minimize the negative effects of the surgical procedures occurring within the brain tissue, including implantation of neural electrodes [9]. To prevent the negative effects resulting from the exposition of the whole body to high dosages of dexamethasone, local delivery of drug at the implant / tissue interface appears as a promising option. As summarized by Aqrawe et al [10], this concept can be easily implemented by the application of drug-loaded conducting polymer matrix as a bioactive coating for the neural electrodes, providing the simultaneous decrease in the risk of inflammatory response and enhancement in the electrical communication between neural tissue and electrode.
Several conducting polymers, including polypyrrole and polyterthiophene, have been already applied as the carriers for dexamethasone. Polypyrrole, one of the most extensively researched drug-carrier among conducting polymers, was found to possess low drug capacity in the range from 6 µg/cm² [11] to 16 µg/cm² [12]. Stevenson et al [13] showed that the amount of dexamethasone released from polyterthiophene exceeded the therapeutic levels, reaching up to 80 µg/cm². Due to its chemical structure derived from polypyrrole and the regularity of structure (polymerization in the 2- and 5-position) resembling polyterthiophene, poly (3, 4-ethylenedioxy)pyrrole (PEDOP), is supposed to possess superior physicochemical properties and higher drug capacity than both aforementioned compounds [14]. This is why PEDOP is believed to be a promising candidate in a role of a controlled drug delivery matrix, especially for the negatively charged dexamethasone.

Recently, it has been shown that PEDOP can serve as an efficient drug-carrier for ibuprofen [15]. Ibuprofen was, however, treated more like a model drug than a real therapeutic agent. In this paper, the more potent drug, dexamethasone, is chosen in order to ensure than the released amounts of drug will have the desired therapeutic effects. It is presented how through the careful choice of the electropolymerization conditions, mainly the concentration of drug in electrolytic solution, the drug capacity and the release modes of conducting polymer matrices can be tailored. Dexamethasone was immobilized through the in situ method basing on cyclic voltammetry. The obtained PEDOP/Dex matrices were analyzed in terms of their electrochemical performance (charge storage capacity), surface morphology, surface chemistry and drug capacity, showing the high variability and tunability of these properties. Release studies were performed for three different modes, i.e. Dex was spontaneously eluted, released potentiodynamically and potentiostatically.

2. Materials and methods

2.1. Materials

3, 4-ethylenedioxy)pyrrole, EDOP (2% w/v in THF, Sigma-Aldrich), Dexamethasone 21-phosphate disodium salt, Dex (≥ 98%, Sigma-Aldrich), potassium chloride (BioReagent, ≥ 99.0%, Sigma Aldrich), sodium chloride (BioReagent, ≥ 99.0%, Sigma Aldrich), disodium hydrogen phosphate (BioReagent, ≥ 99.0%, Sigma Aldrich), potassium dihydrogen phosphate (99.0%, Sigma Aldrich) were used as received. Grade 1 (R > 10 MΩ·cm⁻¹) deionized water was employed as solvent.

2.2. Drug immobilization

CH Instruments 620a Electrochemical Workstation was used to perform electrochemical immobilization procedure in a three-electrode set-up consisting of a Pt foil working electrode (1 cm², 0.5 mm thickness, 99.99% trace metals basis), Ag/AgCl reference electrode and a Pt foil counter electrode. The process of drug immobilization was based on electrochemical polymerization of monomer, EDOP (5 mM) in phosphate buffer saline solution (PBS, 0.15 M NaCl, 0.0025 M KCl, 0.01 M Na₂HPO₄, 0.002 M KH₂PO₄, pH = 7.4) containing dexamethasone 21-phosphate disodium salt (Dex) (0 mM – 100 mM). The polymerization was performed in the potential range from -0.3 V to 0.8 V (vs. Ag/AgCl) within 25 CV cycles at a scan rate of 0.1 V/s. This potential range has been found to be non-destructive for dexamethasone.

2.3. Matrix characterization

The voltammetric experiments were performed using CHI620a in the same three-electrode electrochemical system as described earlier. Cyclic voltammetric (CV) scans were carried out in PBS solution, in the potential range from -0.3 V to 0.8 V (vs. Ag/AgCl) at a scan rate of 0.1 V/s during 3 CV cycles. Cyclic voltammograms were used to determine charge storage capacity (CSC), calculated as the electric charge integrated under corresponding CV curve during one CV cycle [16]:

\[ CSC = \int_{t_1}^{t_2} I(t)dt \]
where $t_1$ is the beginning of CV cycle, $t_2$ is the end of CV cycle, $I$ is the current.

The chemical structure of PEDOP and PEDOP/Dex was characterized using IR Perkin Elmer Spectrum Two spectrometer. IR spectra of Dex, PEDOP and PEDOP/Dex were acquired in the range between 1200 and 1750 cm$^{-1}$ using Diamond UATR accessory. The surface morphology of samples was studied using a Phenom Pro-X scanning electron microscope operating at 10 kV.

2.4. Drug release
Dex release from PEDOP matrix was carried out in PBS solution. Drug concentration was determined through time-resolved UV/Vis spectroscopy (HP 8453 Spectrophotometer) with the use of a calibration curve plotted for absorbance at $\lambda_{\max} = 240$ nm versus drug concentration ($y = 8.43 \cdot x$, $R^2 = 0.991$). Open circuit conditions were used for the spontaneous release process, while electrically-triggered drug release was performed by applying 5 CV cycles between -0.5 V and 0.3 V (vs. Ag/AgCl) at a scan rate of 0.1 V/s (potentiodynamic release) and a reduction potential of -0.5 V (vs. Ag/AgCl) for 600 s (potentiostatic release). The range of potentials has been determined basing on the optimization procedure for PEDOP [15], which showed the highest drug release occurring at -0.5 V.

3. Results and discussion

3.1. Electrochemical performance
As it has been shown by Svirskis et al [17], the in situ method of drug immobilization, in which conducting polymer matrix is electrochemically polymerized from the solution containing drug molecules, is often applied in the formation of drug-loaded conducting materials. If the drug-to-be-immobilized is of an ionic nature, preferably anionic, it can serve as a counter ion for the positively charged polymeric chain and be reversibly immobilized via ionic interactions. The application of cyclic voltammetry as an electropolymerization technique allows to observe the formation of drug-loaded polymer layer, as it is presented in figure 1(a), where the gradually increasing currents confirm the formation of a conductive deposit.

The common problem associated with the application of conducting polymers as drug delivery systems is the optimization of drug content to maximize drug capacity of matrix and maintain its electrochemical properties. While drug capacity can be determined in the release experiments, the use of cyclic voltammetry as the electropolymerization technique enables to assess the electrochemical parameters, such as charge storage capacity (CSC), directly from CV curves. Such set of voltammograms recorded for different Dex concentrations is presented in figure 1(b). It is evident that at the same number of potential scans, the final level of the resulting currents is lower in case of PEDOP/Dex (100 mM) than for pristine PEDOP or PEDOP/Dex (5 mM). The same can be observed when CV curves are integrated and CSC is calculated (figure 1(c)). The 30% decrease in CSC is observed when the concentration of Dex in electropolymerization solution is increased from 5 mM to 100 mM. This decrease in electrochemical performance confirms that Dex concentration of 100 mM can be considered as the upper threshold concentration above which electrochemical properties of conducting polymer matrix cannot be maintained. What is interesting, the enhancing effect of small quantities of drug (5 mM) on the electrochemical performance could be seen. This effect is supposed to originate from the increase in chain separation of the growing chain in a similar way to other bulky dopants, such as for ibuprofen-doped PEDOP [15].

The FT-IR spectra of PEDOP/Dex (figure 1(d)) performed prior to the controlled release studies proved that Dex had been incorporated into PEDOP matrix. Characteristic for Dex peaks at 1715 cm$^{-1}$, 1449 cm$^{-1}$, 1240 cm$^{-1}$, as well as the strong carbonyl signal at 1667 cm$^{-1}$ [12] were observed in the spectra of PEDOP/Dex. The intensity of signals was found to increase with the increasing concentration of Dex, showing the highest content of this drug on the surface of PEDOP/Dex (100 mM). SEM images of PEDOP and PEDOP/Dex (figure 2) evidence the discrepancy between the surface morphologies of samples, confirming the formation of a thin and non-continuous conducting polymer deposit in case of PEDOP/Dex (100 mM) matrix.
Figure 1. Typical CVs of EDOP polymerization in the presence of Dex (10 mM) (a), CVs of 25th cycle of polymerization for different Dex concentrations (b), the comparison of CSC (c) and FTIR spectra of PEDOP and PEDOP/Dex matrices (d).

Figure 2. SEM images of PEDOP and different PEDOP/Dex matrices.
3.2. Electrically-triggered drug release
Since conducting polymers are electrically responsive materials, the electrical trigger in the form of potential or current stimulus is able to change the oxidation state of matrix causing drug release. Among few types of electrical stimulation techniques, two modes are considered as the most effective, i.e. potentiodynamic mode realized via cyclic voltammetry and potentiostatic mode realized via chronoamperometry. Cyclic linear potential sweep in potentiodynamic mode (figure 3(a)) allows the matrix to release drug when it is reduced and to uptake the anions from the environment, mainly chlorides and phosphates, when it is oxidized. In this way the neutral character of matrix is maintained and the process of release is not supposed to have any deteriorating effect on the integrity of matrix. The amount of released drug is controlled through the changes in potential range and number of CV cycles. Potentiostatic process, on the other hand, consists of the constant application of a negative potential (figure 3(b)) resulting in the reduction of polymer matrix. Drug release is controlled by the magnitude of potential applied and time of process. Although longer release times and more negative potentials can increase the release rate, they pose a serious threat to the matrix itself, because constantly reduced matrix is prone to destruction. In this study, potentiodynamic method is used as a preferential release technique, and the potentiostatic method is applied to verify the presence of traces of drugs that have not been released in the potentiodynamic mode.

![Figure 3](image-url)

**Figure 3.** Typical curves of potentiodynamic (5th CV cycle) (a) and potentiostatic (b) release.

3.3. Drug capacity of PEDOP/Dex
The absorbance peak at 240 nm (figure 4(a)) was used to monitor the release of dexamethasone form PEDOP/Dex matrices in different release modes. The achievable concentrations of Dex released via spontaneous and two electrically-triggered modes as a function of Dex concentration in electropolymerization solution (figure 4(b)) show the substantial increase in drug capacity of PEDOP/Dex with increasing amounts of Dex. The cumulative release, being the sum of Dex concentrations released via all three modes, is increasing from 23 μM up to 116 μM when the concentration of Dex in electrolytic solution is increased from 5 mM to 100 mM. It shows that by the careful choice of electropolymerization conditions, mainly Dex concentration, it is possible to produce PEDOP/Dex matrices with a defined drug capacity tailored to the specific needs. What is more, the amount of drug released under all release modes exceeds the therapeutic levels of Dex, which is effective at the concentrations of 0.2 – 0.68 μmol [17]. In this work, up to 116 μM was released from PEDOP/Dex(100 mM), much higher than compared with previously reported polypyrrole/Dex (10 μmol) [12] and polyterthiophene/Dex (50 μmol) [13].
Apart from the differences in total drug capacity, the variation in drug concentration can have the effect on the efficiency of different release modes, both spontaneous and electrically triggered. It can be observed that while the amounts of drug released from PEDOP/Dex (5 mM) via three different modes are almost identical, there is a significant discrepancy in achievable concentrations among the release modes for PEDOP/Dex (50 mM). In the latter, the potentiodynamic release is evidently dominating over both spontaneous and potentiostatic release, showing the superiority of PEDOP/Dex (50 mM) as a controlled release system. The substantial increase in the amount of Dex released via spontaneous mode between PEDOP/Dex (50 mM) and PEDOP/Dex (100 mM) confirms that the high Dex concentrations have the negative effect on the matrix integrity and favors spontaneous drug elution rather than electrically-triggered release.

**Figure 4.** UV-Vis spectrum of Dex with a chemical structure of Dex as the inset (a) and the amounts of Dex released through various modes as a function of Dex concentration in polymerization solution (b).

4. Conclusions
In this study, the electrically-triggered controlled release system based on dexamethasone-loaded PEDOP matrix is described. It is shown that the electropolymerization conditions, mainly the concentration of Dex, can facilitate (at 5 mM) or suppress (at 100 mM) the formation of PEDOP/Dex matrix, as well as have the effect on its electrochemical performance in terms of charge storage capacity. Drug release experiments show that the drug capacity of PEDOP matrix increases with the increase in Dex concentration in the step of matrix synthesis, and higher Dex concentrations make it easier to control the amount of Dex released in an electrically-triggered mode. The results confirm the importance of the careful optimization of immobilization conditions to maximize drug capacity of matrix and maintain its electrochemical properties.

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