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# On-demand Controlled Release of Anti-inflammatory and Analgesic Drugs from Conducting Polymer Films to Aid in Wound Healing*

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*Abstract*—**An electronically-controlled drug delivery system (eDDS) for the on-demand release of anti-inflammatory, anti-microbial and analgesic agents to aid in wound healing is currently under development. The loading of several drugs into conductive polymer films and their subsequent on-demand, controlled release upon application of an electrical potential to the polymer film has been demonstrated. The loading and release (active and passive) of Ibuprofen sodium salt – a negatively charged analgesic and anti-inflammatory agent – from polypyrrole films is described. Major challenges identified include precise control over drug loading and passive release from the conducting polymers in the absence of an applied potential.**

## I. Introduction

The process of wound healing is comprised of a complex series of events, which can be hampered by infection and biofilm formation [1]. The on-demand controlled release of drugs that inhibit biofilm formation, while also reducing inflammation and pain would be beneficial to the wound healing process. Electroactive polymers (EAP) are a special class of polymers that respond in a number of ways to the application of an electrical potential. The applied potential results in a change in the chemical and physical states of the polymer that impacts conductivity, surface energy and pore sizes. Well-known examples of EAPs, some of which can be made highly conductive include polyaniline [2,3,4], polypyrrole, polythiophene and PEDOT. We are currently developing an electronically-controlled drug delivery system (eDDS) to load charged drugs into EAPs that can subsequently be released upon application of either an oxidizing or reducing potential depending on the polymer, the drug and the charge on the drug. Drugs of interest are those that have shown an ability to enhance wound healing and thus far include antibiotic, analgesic and anti-inflammatory agents. The analgesic and anti-inflammatory drug Ibuprofen has previously been shown to be effective at significantly reducing the activity of matrix metalloproteinases [5,6] that, during chronic inflammation, compromise the ability of the wound to heal properly and can lead to chronic wound pathogenesis [7]. Here we describe the on-demand, electronically-controlled loading and release of Ibuprofen sodium salt from highly porous, high surface area, biocompatible polypyrrole EAPs electrodeposited onto carbon cloth electrodes.

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## II. Materials and Methods

### A. Electrochemical Polymerization

Films were generated using a CH Potentiostat (CH Instruments, Inc., Austin, TX, USA) in a three-electrode configuration at 0.9V versus a reference electrode. Using a Ag/AgCl reference electrode, a stainless steel counter electrode, and a carbon fiber cloth as a working electrode, films were polymerized in an aqueous solution of 1M KCl, 0.15M Ibuprofen sodium (Sigma-Aldrich, St. Louis, MO, USA), and 0.3M distilled pyrrole. For the burst release experiment described below, the charge used to generate the film was 71.4 C. The step release films were prepared using 2.8 C of charge. Films were rinsed in 2L of deionized $H_2O$ with sonication for 10 minutes and then placed in a fresh 2L of deionized $H_2O$ and rinsed for 20 minutes.

### B. Burst Ibuprofen Sodium Release

The buffer used for burst release was 0.01 M phosphate buffered saline (PBS) with a pH of 7.4. The burst release was performed using a two-electrode configuration of the Gamry MultEchem potentiostat (Gamry Instruments, Warminster, PA, USA) with a voltage drop of -3V between the working and counter (carbon fiber without polymer) electrodes for 10 minutes. Release was observed in real time using an Ocean Optics USB2000+ in combination with a Mikropack DH-2000 UV-Vis light source and the Ocean Optics SpectraSuite software. The release of Ibuprofen sodium was monitored and plotted as absorbance at a wavelength of 264 nm.

### C. Step Ibuprofen Sodium Release

Step release of Ibuprofen sodium was performed using a three-electrode (Ag/AgCl as reference) configuration of the Gamry MultEchem potentiostat with a voltage of 0.5V applied for 400s and then -0.5V applied for 40s to the working electrode versus Ag/AgCl for 5 complete cycles using carbon fiber without polymer as a counter electrode. Monitoring of release was performed as described in Section II.B.

### D. Cytotoxicity Analysis

For cytotoxicity testing, polypyrrole films and Ibuprofen sodium loaded polypyrrole films were prepared using a CH Potentiostat in a three-electrode system with a Ag/AgCl reference electrode. The films were polymerized in an

aqueous solution of 1M KCl, 0.02 M Ibuprofen sodium, and 0.3M distilled pyrrole at 0.9V versus the reference electrode using a carbon fiber cloth as the working electrode and a stainless steel counter electrode until 12 Coulombs were reached. The evaluation was performed using RD cells (ATCC: CCL-136) provided by the Center for Biomedical and Life Sciences (CBLS) at Missouri State University and evaluated using an MTT assay. Drug was released in a 2-electrode system with a carbon fiber cloth counter electrode by applying a -1.5V constant potential to the working electrode.

*E. Factors impacting Ibuprofen loading and release*

A systematic study *via* design of experiments (DOE) was conducted to predict the impact of various factors on passive and active release of ibuprofen sodium from polypyrrole (PPy) films in a 2-electrode system. Factors of interest included: a) Ibuprofen sodium concentration during e-polymerization (0.02 – 0.15 M); b) electropolymerization charge (5 – 100 C); c) applied release voltage (-1.5 – -3.2 V); and d) release counter electrode type (plain carbon cloth or carbon cloth with PPy). The effect of each of these factors on the following was investigated: 1) amount of passively released Ibuprofen in 10 min (measured in mg); 2) amount of actively released Ibuprofen in 10 min (mg); 3) residual Ibuprofen in the film (mg); and 4) total Ibuprofen loaded (mg). The total Ibuprofen loaded was calculated as the sum of the quantities of Ibuprofen that were passively released, actively released and remaining in the PPy film. Ibuprofen was loaded into the PPy film and rinsed by a similar procedure as described in (II. A). The Ibuprofen sodium concentration and electropolymerization (e-polymerization) charge were varied to control the amount loaded. Individual films were then immersed in 30 ml 0.01 M PBS solution (pH 7.4). A 1.5 ml aliquot was taken after 10 min passive release. A negative voltage was then applied to the working electrode for 10 min to actively release Ibuprofen sodium. Another 1.5 ml aliquot was taken at the end of the 10 min active release period. The conducting polymer electrode was then soaked in 30 ml KOH (1 M) to release any residual Ibuprofen remaining in the polypyrrole film. Ibuprofen quantities were measured using HPLC (Varian binary pump 212LC, Varian ProStar325 UV-Vis, Varian MS500 ion trap). The fitting model used was response surface methodology (RSM). The DOE comprised 16 experiments plus 1 repeat for each experiment and was conducted using JMP 9.0 statistical software (SAS, Cary, NC, USA).

## III. Results and Discussion

Electrochemical polymerization of the inherently conducting polymer, polypyrrole, results in the formation of high surface area films as evidenced by scanning electron microscopy (SEM) images (Fig. 1). The high surface area of such conducting polymer films is not only a function of the micro- and nano-scale topology of the electrodeposited polymer, but of the porosity as well. The quantity of the EAP deposited and consequently the total surface area available for drug loading can be controlled by the length of time of electrodeposition (total charge passed). The EAP, therefore, offers two advantages that benefit a controlled drug release system – 1) a high surface area that results in the ability to achieve increased drug content; and 2) the ability to switch the oxidation state and surface charge to encourage loading and release. In this study, the analgesic and anti-inflammatory agent, Ibuprofen sodium salt, was loaded into and released from polypyrrole EAP films deposited onto carbon cloth electrodes. By increasing the total charge passed, one can increase the quantity of polypyrrole deposited and consequently the total surface area for drug loading. Using UV-Vis spectrophotometry and a HPLC-MS, the quantities of drug released from the polypyrrole films were determined.

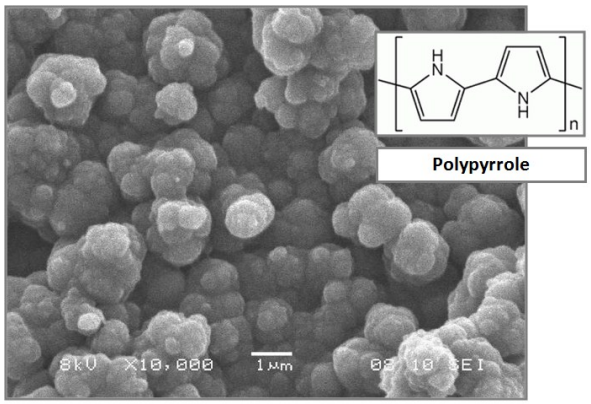



Figure. 1 SEM image (x10K magnification) of electrochemically polymerized polypyrrole deposited on a metal electrode.

*A. Release profiles*

The burst release of Ibuprofen sodium salt into 0.01 M PBS is shown in Fig. 2 (measured using an absorbance wavelength of 264 nm). Upon application of a negatively biased potential (-3V) between the working and counter electrodes, an appreciable increase in the rate of Ibuprofen release was observed (Phase 2) compared to the initial passive release (Phase 1). The rate of release gradually decreases with time, eventually tapering off (Phase 3), and is expected to plateau as the system approaches equilibrium. Fig. 3A shows the voltage and current profiles associated with step release. Fig. 3B shows the release of the Ibuprofen as measured using absorbance at a wavelength of 264 nm.

Some passive release occurs during immersion of the polymer film within the PBS. However, the rate of release increases with the application of the applied potentials. The rate of active release of Ibuprofen sodium subsequent to the first negative potential bias was approximately 10 times greater than the initial passive release (Figures 2 and 3).

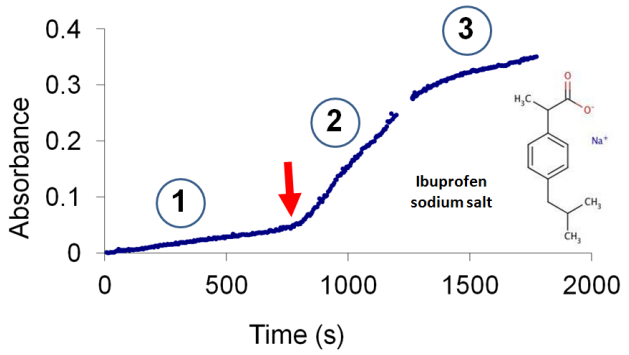
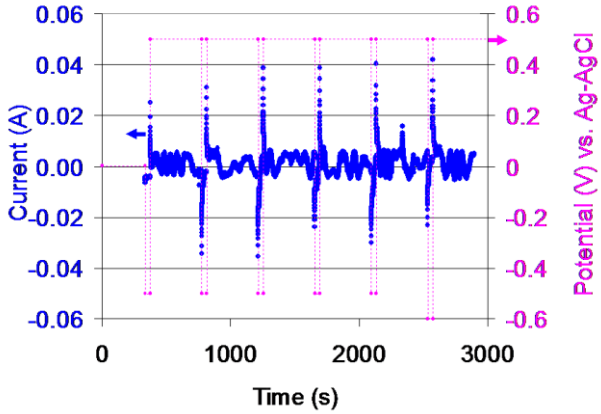



Figure 2: Absorbance profile at 264 nm indicating burst release of Ibuprofen sodium salt into 0.01M PBS. The arrow indicates the point of the applied reducing potential. Phase 1 of the plot indicates passive release. Upon application of a reducing (negative) potential, an increase in the rate of Ibuprofen release is observed (Phase 2). The rate of release gradually decreases with time, eventually tapering off (Phase 3).

An important challenge currently is to reduce the overall passive release of such systems. In both burst and step release, the release profiles indicate control of the system using applied potentials. Further work is needed, but the outlook of on-demand controlled release as a method of drug delivery via EAPs is promising.

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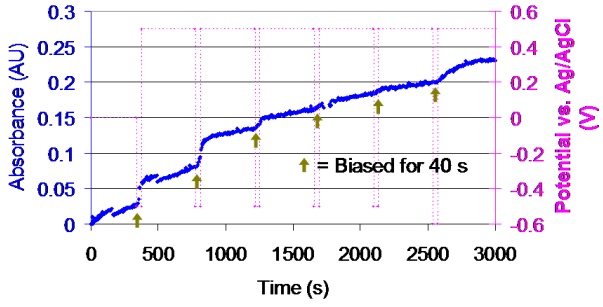


B

Figure 3: (A) Voltage profile and current response associated with Ibuprofen sodium salt release into 0.01 M PBS. (B) Release profile of Ibuprofen sodium salt as measured by UV absorbance.

*B. Cytotoxicity Analysis*

The cytotoxicity of the polypyrrole and the Ibuprofen sodium loaded polypyrrole films was investigated. In both instances, the films proved to be noncytoxic to the RD cells investigated (≥85% cell viability based on a modified MTT assay) under both passive and active release conditions.

*C. Design of Experiments (DOE)*

Figure 4 shows the predictive model and effects of each factor investigated on passive release, active release, residual and total loading. The coefficient of determination, $R^2$, indicates how well the experimental data fits to the prescribed model. An ideal model has an $R^2$ value that approaches 1.

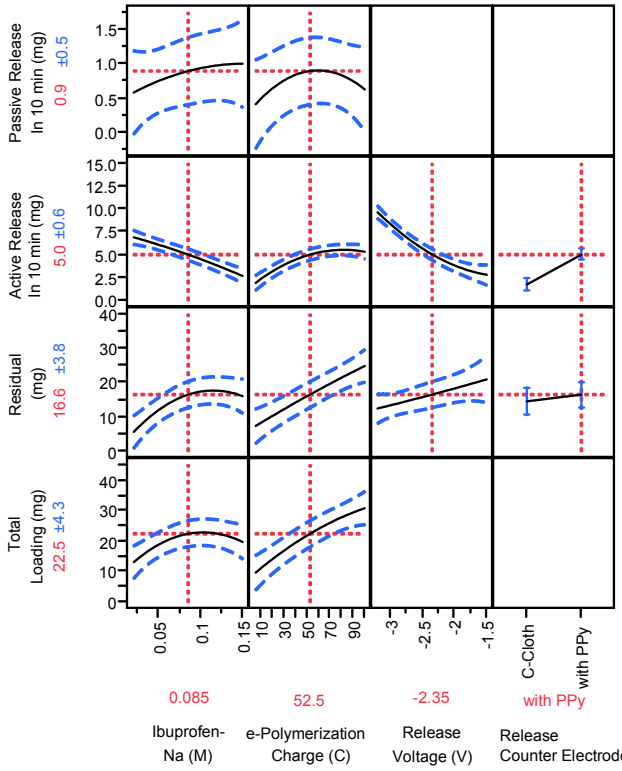


Figure 4. Predictive model and effects of various factors on Ibuprofen salt release.

*Passive release ($R^2$ = 0.52)*

The $R^2$ value in this case was somewhat low, indicating that the model was not a very good fit. This, however, is most likely due to the very short period of time during which passive release was allowed to occur (10 mins). This short time span would mean that very small quantities of Ibuprofen sodium would have been released and consequently rather large error bars would result. Based on the trends in the data, it was found that increasing the concentration of Ibuprofen salt used for loading into the film was associated with greater quantities that were passively released. This would be a reasonable assumption because high concentrations of Ibuprofen sodium in the solution during electropolymerization would mean higher

concentrations in the final polymerized conducting polymer film. The resulting higher concentrations of Ibuprofen in the film would mean greater diffusion rates once the loaded films are transferred to Ibuprofen-free solutions. Electropolymerization charge (C), an indication of the total polymer quantity allowed to polymerize at the working electrode, was identified as a significant factor. The greater the amount of charge passed, the greater the quantity of polypyrrole deposited (greater polymer thicknesses) at the working electrode. Based on the DOE results, it was found that an optimal charge of 50 C resulted in the greatest quantity of Ibuprofen sodium released. At values greater than 50 C, the quantity of Ibuprofen sodium that is passively released decreases. This is not unexpected as thicker conducting polymer films would result in a greater degree of difficulty for Ibuprofen buried within the film to diffuse through the polymer and out into the surrounding media.

*Active release ($R^2$ = 0.99)*

All four factors were found to be significant to active release. Since the goal is to maximize active release of the loaded drug molecules, the most important factors that can be influenced to achieve this are to 1) increase the e-polymerization charge (leads to higher polymer content and, likely, higher total surface area for Ibuprofen sodium loading and their charge interactions with the polymer backbone) 2) apply more negative potentials (encourages electrophoretic effects following conducting polymer reduction); 3) choose PPy coated carbon cloth versus plain carbon cloth as the counter electrode (increases the current between the working and counter electrodes and consequently the amount of drug released) and 4) decrease the Ibuprofen sodium concentrations used during loading, a final point which seems counterintuitive and is at the moment unclear. Regarding point (3), electropolymerization of conducting polymers on electrode surfaces results in an increased electroactive surface area and lower electrode-solution interfacial impedance. This leads to higher currents between the working and counter electrodes for a given applied potential. The result of these higher currents is an increase in the rate of release of Ibuprofen sodium from the polymer under applied potentials.

*Residual Ibuprofen ($R^2$ = 0.96)*

The model also revealed that there would be more residual Ibuprofen in the conducting polymer films if they were prepared in the presence of higher concentrations of Ibuprofen sodium, higher e-polymerization charge, and more positive applied release potentials.

*Total Loading ($R^2$ = 0.95)*

The total loading simply reflects the sum of the passively and actively released Ibuprofen and the residual amount remaining in the film at the end of the experiment. The amount of Ibuprofen salt in the PPy films increased with increasing Ibuprofen sodium solution concentrations and with increased charge passed during the electropolymerization process.

## IV. Conclusion

The on-demand controlled release of Ibuprofen sodium salt from polypyrrole EAP films has been demonstrated. The conducting polymer, polypyrrole, as well as Ibuprofen sodium salt loaded polypyrrole were revealed to be noncytotoxic. It was found that a number of factors impact the quantity of Ibuprofen salt that is actively released from the conducting polymer films, particularly the amount of charge passed during electropolymerization (which reflects the thickness of the polymer film), the applied release potential and the choice of the counter electrode. Increased active release of Ibuprofen sodium is associated with increased charge passed (increased polymer thickness), more negative applied potentials (larger electrophoretic effects) and high surface area PPy coated carbon cloth counter electrodes (higher currents).

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