Electrically Triggered Small Molecule Release from Poly (*N*-Isopropylacrylamide-co-Acrylic Acid) Microgel-Modified Electrodes

*Wenwen Xu, Yingnan Zhang, Yongfeng Gao, Michael J. Serpe**

Prof. M. J. Serpe, W. Xu, Y. Zhang, Y. Gao

Department of Chemistry, University of Alberta

Edmonton, Alberta, T6G 2G2, Canada

*Email: michael.serpe@ualberta.ca

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Abstract: A monolithic layer of poly(*N*-isopropylacrylamide-co-acrylic acid) (pNIPAm-co-AAc) microgels was deposited on a Au electrode and used for electrically triggered release of the small molecule crystal violet (CV), which was used as a model drug. CV was loaded into the surface bound microgels by exposing them to a CV solution at pH 6.5, where the microgels are negatively charged and the CV is positively charged. The electrostatic attraction holds the CV inside of the microgels, while a decrease of the solution pH can neutralize the microgels and allow for CV release. In this investigation, we show that when CV-loaded microgels are deposited on the anode in an electrochemical cell, and an appropriate voltage applied, there is a decrease in the solution pH near the anode surface that allows for CV release. We also show that removing the applied potential allows the solution pH near the anode to return to pH 6.5, which halts the release. We show that the release rate from the microgel-modified anodes could be controlled by the magnitude of the applied voltage and by pulsing the applied voltage or

applying a continuous voltage. Furthermore, we showed that the microgel-modified anodes can be reloaded with CV and used to release CV to a system many times. Such devices could be used as implantable drug delivery devices, as well as for industrial applications where small molecules need to be released to systems in response its chemical status.

Introduction

Devices capable of loading small molecule therapeutic drugs, while allowing for their controlled/triggered release to a system can have important positive impacts on human health care and disease treatment.[1-2] For example, controlled/triggered drug delivery devices have the ability to release beneficial small molecules to a system only when they are needed, and at the rate/dosage that is required to keep the concentration of the therapeutic agent in the desired range for long periods of time.[3-4] This is quite different than traditional drug delivery methods (oral delivery or injection), which yield a maximum concentration shortly after administration that decays to a range below the therapeutic range over time.[5] To achieve the desired benefit from the treatment, another dose of the drug needs to be administered to again bring the concentration of the therapeutic into the desired range. Due to the many potential benefits that come with controlled/triggered drug delivery devices, significant research has gone into their development for many years.[6-7]

In previous studies, various materials have been used to construct controlled drug delivery devices, such as graphene-based scaffolds,[8-9] magnetic nanoparticles,[10-11] liposomes,[12] and hydrogels.[13-16] Most important for this investigation are hydrogels, which are crosslinked three-dimensional polymer networks that are able to absorb substantial amounts of water, e.g., up to a thousand times their dry mass.[17-18] Generally speaking, since hydrogels are soft materials, they

are better tolerated by the body, and lead to a low amount of inflammation and irritation.[19-20] Their chemistry can be easily altered to render them biocompatible, non-toxic, and biodegradable that allows them to be cleared from the body after performing their function.[21-22] To allow for an even greater amount of functionality, metal nanoparticles,[2] carbon nanotubes,[23] and quantum dots can be incorporated into the hydrogels.[24]

To realize controlled drug release from hydrogels, their chemistry can be modified to allow them to respond to temperature, light, and electricity.[25-27] Electrical stimulation is potentially an efficient method to precisely release drugs from materials in a controlled manner due to the ability to very finely control the magnitude and frequency of applied voltage/current. Furthermore, electronic equipment is readily miniaturized to allow for its use *in vivo.* In fact, electrically stimulated drug delivery products have previously been commercialized, for example the iontophoresis device from IOMED Inc. can deliver drugs through the skin by application of a low level current.[28] Thus, the development of hydrogels capable of electrically stimulated drug release can combine the benefits of both hydrogels and electrically stimulated drug release.[29-30]

Electroactive hydrogels are typically generated from monomer units that contain ionizable groups, which can modulate the solvation state of the hydrogels in response to an electric field and lead to drug release.[31] For example, when an electric field is applied to a negatively charged hydrogel placed between two electrodes, the free cations will move to the cathode while the polyanion will be pulled toward anode via electrostatic interactions. As a result, such a polyanion gel will deswell near the anode and provide the driving force for drug release.[32] In another example, a mixture of polymer solutions consisting of poly(ethyloxazoline) (PEOx) and poly(methacrylic acid) (PMMA) can form complexes due to hydrogen bonding between oxazoline and carboxylic moieties only at pH <5. When the solution pH is >5, the hydrogen

bonds will be broken resulting in dissolution of the polymer complex and release of drug from the network.

Hydrogels with "macroscopic" dimensions (100's of μm), such as those described above, have been extensively studied, although there are certain disadvantages to their use. For example, larger materials are painful to implant into the body, have relatively slow response kinetics that ultimately limits release rates, and typically exhibit poor mechanical properties. Therefore, a variety of new approaches to achieve controlled/triggered drug delivery have emerged.[33] For instance, injectable/*in situ* gelling hydrogels have received a lot of attention. Using this approach, a mixture of precursor polymer solution with low viscosity and drug can be injected to targeted areas in a minimally invasive manner. After injection, gelation occurs through physical/chemical crosslinking in the physiological environment. Such a three dimensional gel network can trap the drug inside and also acts as a diffusion barrier for the drug, allowing for prolonged drug release.[13, 34] Additionally, nanometer and micrometer-scale hydrogels have been used for controlled/triggered drug delivery due to their many advantages, e.g., ease of injection, relatively fast response (and release kinetics), and easy chemical modification to allow for complex delivery profiles. [14, 35]

In this investigation, stimuli-responsive polymers were used to achieve controlled/triggered drug delivery. Of the various stimuli-responsive polymers, poly (*N*-isopropylacrylamide) (pNIPAm) has been the most extensively studied, primarily due to its thermoresponsive behavior that can be tuned to be near physiologically relevant temperatures.[36] Specifically, pNIPAm exhibits a lower critical solution temperature (LCST) of ~32 ºC. As a result, when the solution temperature rises above the LCST, the polymer chains transition from a hydrophilic random coil state (extended) to a hydrophobic globular state (collapsed). PNIPAm can also be crosslinked to

form hydrogels and micro/nano size hydrogel particles (microgels and nanogels, respectively) via precipitation polymerization.[37] Furthermore, by incorporating other comonomers into pNIPAm, they can be made to respond to various other stimuli. Acrylic acid (AAc) is a comonomer that is used quite frequently as a comonomer, and imparts pH responsivity to the pNIPAm. This is due to AAc being a weak acid (pK_a = 4.25), which is deprotonated at solution pH > 4.25; at this pH pNIPAm-co-AAc microgels are negatively charged and swell due to the Coulombic repulsion between the negative charges and osmotic swelling. At solution pH < 4.25 the AAc is neutral, and are relatively deswollen. Important for the study here is the pH switchable charge that can be exploited for controlled/triggered drug delivery. As we have shown in a previous study, a positively charged model drug crystal violet (CV) can be loaded into pNIPAm-co-AAc microgels at pH > 4.25 (microgel negatively charged) while it could be released by decreasing the pH to < 4.25 (microgels are neutral).[38-39] This pH-dependent loading and release process is shown schematically in Figure 1. While this approach to controlled/triggered drug delivery is useful, it requires the pH of the solution to be manually adjusted to release CV, which limits the practical applications.

To expand the utility of pH-triggered drug delivery, we show here that electrical stimulation of pNIPAm-co-AAc microgel-based devices can be used to release a small molecule model drug to a system on demand. Specifically, CV-loaded microgels were immobilized on a Au electrode and used as an anode in an electrochemical cell, while a bare Au electrode was used as a cathode and both were exposed to a pH 6.5 solution. It is well known that the application of a suitable potential between two electrodes in water leads to water electrolysis (reduction potential for water is 1.23V vs SHE at pH 7), which results in a decrease of solution pH near the anode. Here, we show that the degree of ionization of the pNIPAm-co-AAc microgels can be controlled by

application of a suitable potential between the cathode and anode, which can disrupt the electrostatic interactions holding the positively charged model drug CV in the microgels and lead to its release. The magnitude and speed of the pH change can be controlled by the applied potential, which in turn can control the release of the CV in a real-time fashion. In addition, previous reports have shown that charged drugs may undergo electrophoresis in an external field, which may alter the release profile.[28] For example, since CV is a positively charged small molecule, it is possible that CV could migrate away from the anode, accelerating the release process. While we do hypothesize that we observe electrophoresis-accelerated release under certain release conditions in this investigation, a detailed study of this process is not presented here, and will be investigated in future work. Overall, we show that the microgel layer deposited on a Au anode in an electrochemical cell can be used to realize real time controlled drug release, which can be subsequently used in theranostic applications.

Results and Discussion

Devices used for electrically stimulated drug release were fabricated as shown schematically in Figure 2. To prepare the Au electrode, 2 nm Cr was deposited on a glass substrate that served as an adhesion layer for the subsequently deposited 50 nm Au layer. Following our previously reported paint-on protocol, a densely packed microgel monolayer was deposited on the Au electrode. In order to allow easy electrical connection of the Au electrode to the power supply, we left one side of the slide unmodified (an area of 0.5 cm × 2.5 cm). Once the microgel layer was deposited on the Au-coated glass slide, the microgels were loaded with CV by exposing them overnight to a solution of CV at pH 6.5. The strong electrostatic interaction between the positively charged CV and negatively charged pNIPAm-co-AAc microgel at pH 6.5 has been

reported previously.[38] In order to remove any CV nonspecifically absorbed/adsorbed to the microgels and/or Au electrode, they were soaked in pH 6.5 solution for 2 h before use. We note that the resultant slides exhibited a purple color, while slides with no microgels attached that underwent the same treatment exhibited no obseravable color change. Next, the as-prepared slide was inserted into a homemade glass cell and exposed to 20 mL of pH 6.5 solution with a bare Au electrode used as the counterelectrode; the slides were used as the anode and cathode, respectively. Each electrode was connected to an external power supply that was used to supply DC voltages, while the whole system was sealed with parafilm to prevent solution evaporation. Upon exposure to a proper anodic potential, the pH near the anode drops dramatically due to water electrolysis, which we hypothesize will neutralize the microgel's AAc groups and weaken the CV-microgel interactions and lead to CV expulsion. CV (structure shown in Figure 3(a) was used as a model drug because it is readily avialable, inexpensive, has a high molar absorptivity, and is highly soluble in water. Its favorable solubility in water, and its high molar absorptivity allows the release process to be monitored using UV-Vis spectroscopy. Figure 3(b) shows a typical absorbance spectrum for CV, showing an absorbance maximum at 590 nm. Therefore, by monitoring the absorbance at 590 nm, we can monitor the CV release kinetics.

As we state above, we use water electrolysis to reduce the solution pH near the anode, which we hypothesize can neutralize the negative charges on the microgels, thus weakening the CV-microgel interaction, and allowing CV to be released to solution. Again, this is to replace the need for manually switching the solution pH to trigger release as shown in Figure 1. To demonstrate the electrically-triggered release, we first confirmed that the solution pH in the vicinity of the anode does indeed decrease upon application of appropriate DC electrical potentials. To accomplish this, two bare Au electrodes were connected to a DC power supply,

and a miniature pH electrode was placed near the anode at a distance of ~ 2 mm to monitor the pH change. The water electrolysis potential is ~1.23 V in a pH 7 solution and the potentials we used here were all >1.23 V to ensure efficient water electrolysis. However, we note that the potential should not be too large as this can lead to the Au layer peeling off the glass slide and bubble generation. Therefore, we kept the applied voltage ≤ 4 V for the experiments here. As can be seen in Figure 4, application of the indicated voltages to the electrodes led to a subsequent solution pH decrease near the anode, presumably a result of water electrolysis. Specifically, increasing the magnitude of the applied potential (from 2 V to 4 V) appeared to accelerate the water electrolysis rate that resulted in a larger and slightly faster drop in solution pH near the anode over a pH range of ~ 5.2 to ~ 3.2. Upon removal of the applied potential, the pH quickly changed back to the original bulk solution's pH of 6.5.

Next, we showed that the decrease in solution pH near the anode could trigger the release of CV from the surface-bound microgels. To demonstrate this, we applied different pulsed voltages to the devices to trigger the release of CV from the microgels. Specifically, in one cycle, we applied the external potential for 1 min followed by its removal for 5 min. The on-off cycle was repeated four times. As detailed in the experimental section, we recorded a UV-Vis spectrum of the release solution every 1 min, and used the absorbance value at 590 nm as an indicator of the amount of CV in the solution that was released from the microgels. As can be seen in Figure 5(a), the solution absorbance increased substantially when a voltage was applied to the system, while relatively little was released when no potential was applied. We also note from the data in Figure 5 (a) that more CV could be released to solution in a given time when the magnitude of the applied potential was increased. This clearly demonstrated that the kinetics of the release (i.e., dose) can be controlled by the magnitude of the applied potential. Finally, we note that CV

release was effectively halted when the applied potential was removed from the electrodes, allowing CV release to be turned on and off. The observed electrically stimulated CV release can be explained by taking into account the neutralization of the pNIPAm-co-AAc microgels when the solution pH near the electrode decreases due to water electroysis, which allows for CV release; lower solution pH leads to more AAc neutralization, which should yield enhanced release rates. Although, we also propose that previously observed electrophretic processes can also contribute to the observed release profiles.[28] Specifically, from the data in Figure 5 (a), it is clear that the devices with 4 V applied release faster than the devices with 3 V applied, although the measured solution pH near the anode (Figure 4) is not significantly different. Hence, another release mechanism must be responsible for the enhanced release rate as the anode potential is increased. We hypthesize that it is a combination of AAc neutralization and electrophoretic release that yields the observed behavior

Figure 5(b) shows the cumulative CV release profiles for the devices at the indicated applied voltages. As can be seen, the total release increased when a larger potential was applied to the electrodes. Furthermore, we calculated the release rates from the data in Figure 5(b), by calculating the initial slopes of the release curves for the different applied voltages. As can be seen in Figure 5(c), the release rate increased linearly as the external voltages increased, which can be explained by AAc neutralization and electrophoretic expulsion of CV from the device.

One of the major advantages of electrically stimulated drug delivery is that the magnitude and frequency of the applied potential is very easily programmable such that various release profiles can be achieved for a single device. Thus, we applied various continuous voltages to our electrodes as well as a pulsed voltage and determined respective release profiles. As can be seen in Figure 6, the time to reach a solution absorbance value of ~ 0.08 varied with applied voltage

and the frequency of its application. Specifically, by decreasing the magnitude of the continuously applied voltages (from 4 V to 2 V) a longer time was required to reach a solution absorbance of ~0.08. Furthermore, with the pulse pattern used here ~30 min was required to reach an absorbance of 0.08.[12]

Finally, we showed that the microgels deposited on the electrodes could be used to load and release the small molecule CV multiple times. To demonstrate this, after the first CV release cycle was complete, we resoaked the microgel-coated Au electrode in a CV solution overnight and assembled the same electrochemical cell that was used for all other experiments and monitored the release. As can be seen in Figure 7, the reloaded devices had a release profile that was similar to the first release, which is also similar for further reloading and release experiments (we only show five reloading cycles here).

Conclusion

In this manuscript we showed that a monolithic layer of pNIPAm-co-AAc microgels deposited on a Au-coated surface (anode) can be used as a reservoir for CV, which can be released upon electrical stimulation. We first characterized how the solution pH near the microgel-coated anode surface depends on the magnitude of the potential applied to the electrochemical cell. We showed that the solution pH near the anode surface decreased as a function of the magnitude of the potential applied, which could be used to release CV from CV-loaded pNIPAm-co-AAc microgels. We also showed that the amount of CV released depended on the magnitude and frequency of the applied voltage. Finally, we showed that our devices can be reused multiple times and the reloaded devices showed release profiles similar to the first and all previous releases. Taken together, the results suggest that these devices can be used to control dosages of small molecules to systems in an electrically controlled fashion.

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Experimental Section

Materials: N-isopropylacrylamide (NIPAm) was purchased from TCI (Portland, Oregon) and purified by recrystallization from hexanes (ACS reagent grade, EMD, Gibbstown, NJ) prior to use. N,N'-methylenebisacrylamide (BIS) (99%), acrylic acid (AAc) (99%) , ammonium persulfate (APS) (98+%) were obtained from Aldrich (St. Louis, MO) and were used as received. Deionized (DI) water with a resistivity of 18.2 MΩ·cm was used. Microscope glass slides were and obtained from Fisher Scientific (Ottawa, Ontario) and cut into pieces (25 × 25 mm).

Microgel Synthesis: Microgels were synthesized following previously described protocols. Briefly, a 3-necked round bottom flask was fitted with a reflux condenser, nitrogen inlet, and thermometer, and charged with a solution of NIPAm (10.52 mmol) and BIS (0.702 mmol) in 99 mL deionized water, previously filtered through a 0.2 μm filter. The solution was purged with N_2

and allowed to heat to 70 °C, over ~1 h. AAc (2.81 mmol) was added to the heated reaction mixture in one aliquot. The reaction was then initiated with a solution of APS (0.2 mmol) in 1 mL of deionized water. The reaction was allowed to proceed at 70 °C for 4 h under a blanket of nitrogen gas. The resulting suspension was allowed to cool overnight, and then it was filtered through a Whatman #1 paper filter to remove any large aggregates. The microgel solution was then distributed into centrifuge tubes and purified via centrifugation at ~8300 rcf to form a pellet, followed by removal of the supernatant and resuspension with deionized water; this process was completed 6 times.

Fabrication of electrochemical cell for drug delivery

Au coated coverslips were generated by thermally evaporating 2 nm Cr followed by 50 nm of Au onto a 25 × 25 mm ethanol rinsed and N_2 gas dried glass slide. (Torr International Inc., thermal evaporation system, Model THEUPG, New Windsor, NY). Before microgel deposition, a 2 × 25 mm PDMS film was used to mask one side of the Au coated glass slides such that the power supply can be connected. A 40 µL aliquot of concentrated microgels (obtained via centrifugation of a microgel solution) was added to the substrate and then spread using the side of a micropipet tip at 30 ºC. The microgel solution was allowed to dry completely on the substrate for 2 h with the hot plate temperature set to 35 ºC. After that, the glass slide was rinsed copiously with DI water to remove any excess microgels not bound directly to the Au. The glass slide was then placed into a DI water bath and allowed to incubate overnight on a hot plate set to 30 ºC. Following this step, the substrate was again rinsed with DI water to further remove any microgels not bound directly to the Au substrate surface. The samples were then rinsed with deionized water, dried with N_2, and then soaked into 10 mL 0.04 mg/mL CV solution overnight.

After overnight, CV loaded glass slides were thoroughly washed with DI water and then soaked into pH=6.5 solution for 2 h to remove the excess CV.

The electrochemical cell was constructed as depicted in Figure 2. The two electrodes were placed inside a 3 cm^3 glass cell with a 2 mm wall thickness. The distance between each slide was 2.4 cm. 20 mL of pH 6.5 solution (2 mM ionic strength) was added into the glass cell. The two electrodes were connected to the external power supply. A paraffin film was used to seal the cell to prevent water evaporation and the solution was stirred at 60 rpm. 1 mL solution was transferred by digital pipet into quartz cuvette to monitor the absorption change during the whole process. After the UV-Vis spectrum was acquired, the solution was added back to the release solution to keep the volume constant.

Instrumentation: UV-Vis spectra were obtained using an Agilent 8453 UV−Vis spectrophotometer. pH was measured with a Jenco model 6173 pH meter (San Diego, CA).

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Figures

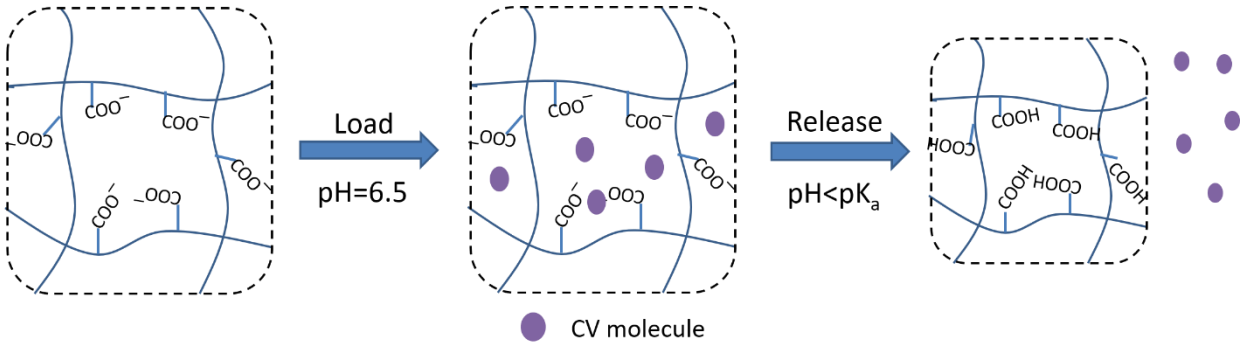

Figure 1. CV is loaded into the pNIPAm-co-AAc microgels at high pH through electrostatic interactions. When the microgel are neutralized the CV can be released.

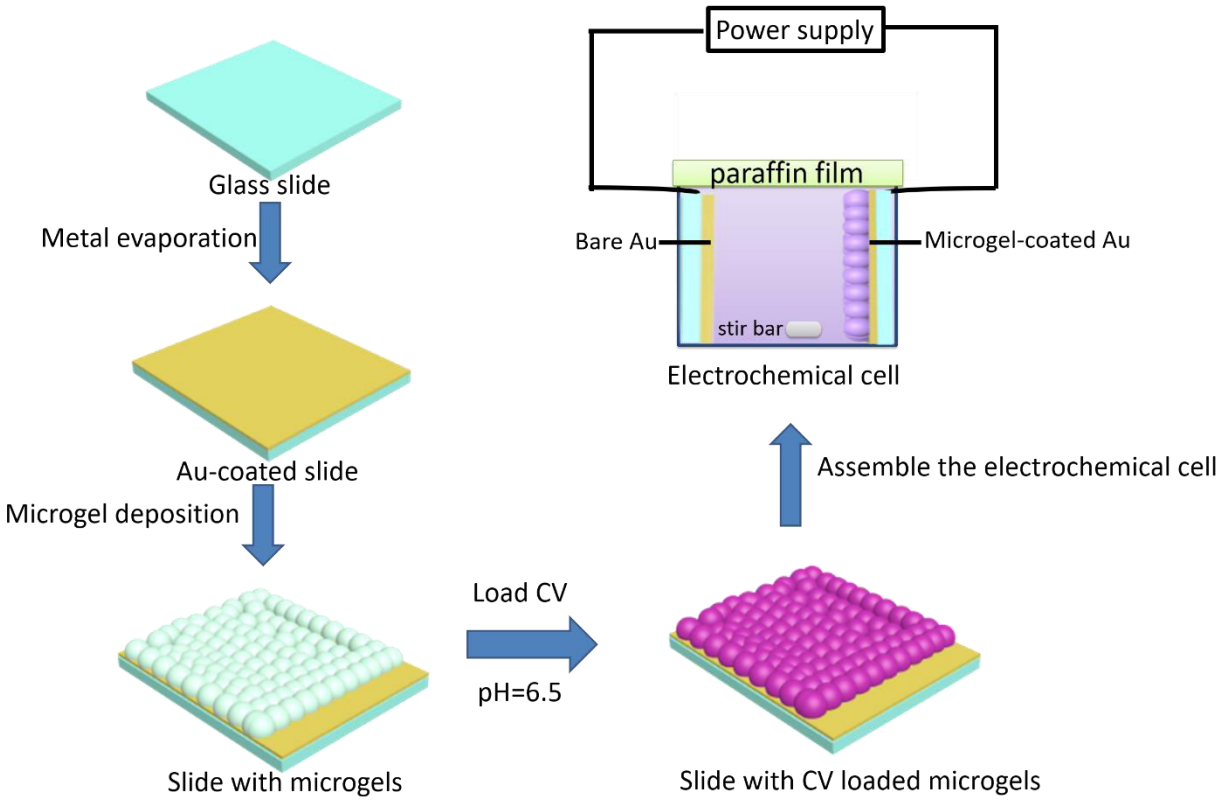

Figure 2. The experimental setup used for studying electically triggered CV release from pNIPAm-co-AAc microgel-coated anodes.

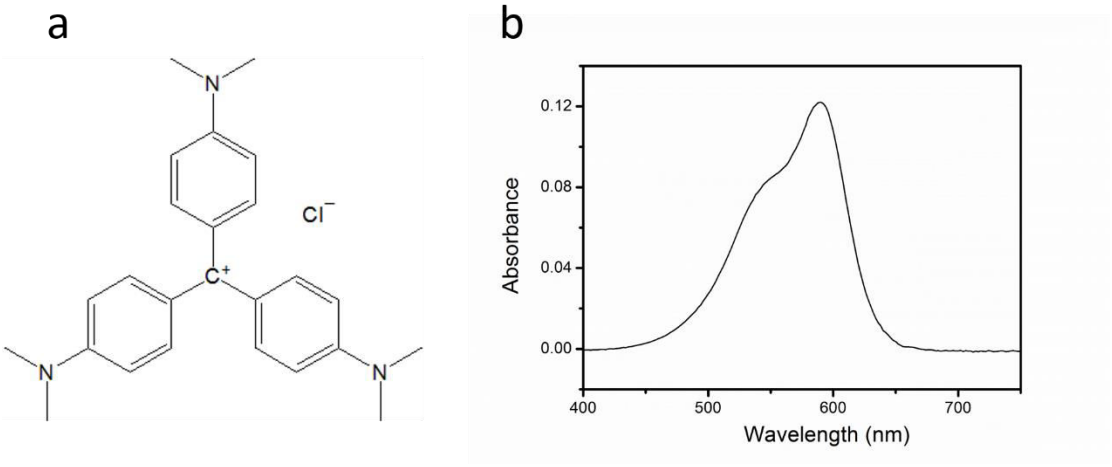

Figure 3 a) The chemical structure of CV; b) The UV-Vis spectrum CV in an aqueous solution

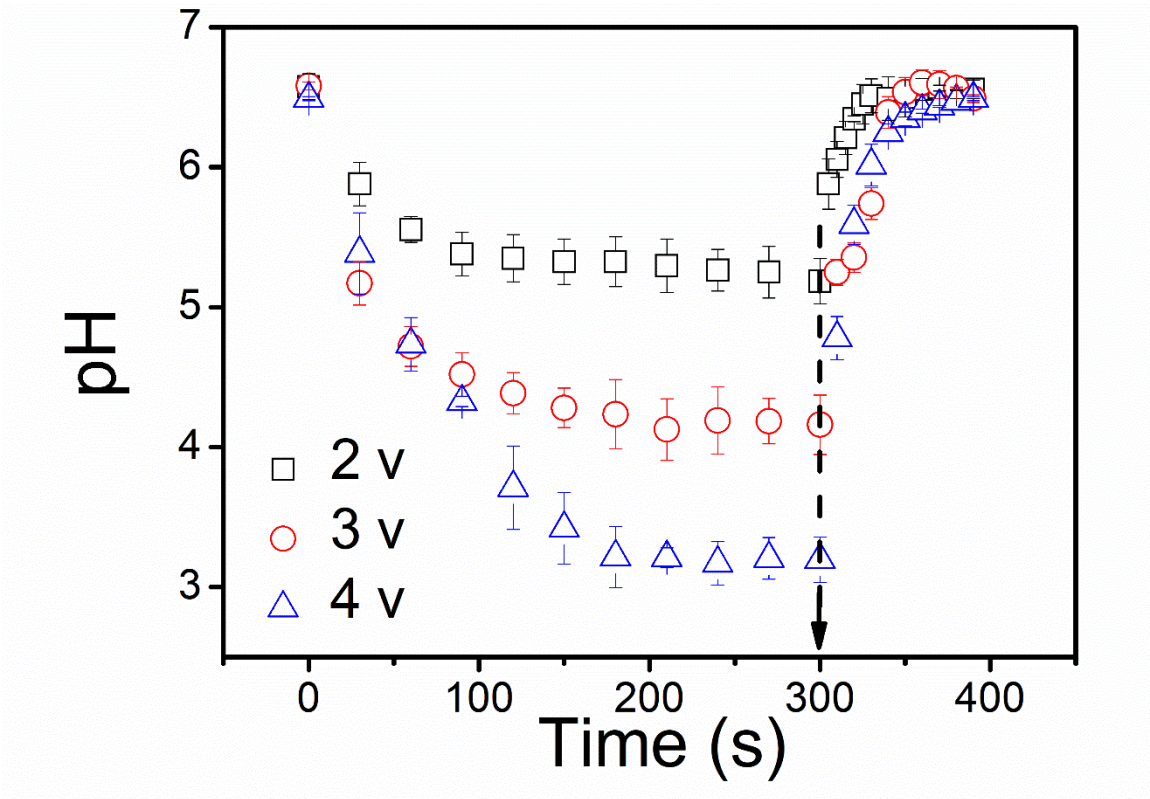

Figure 4. The variation of the solution pH near the anode surface as a function of time for the indicated applied potentials. After 300s (arrow), the potentials was removed. The data points are averages and the error bars are the standard deviations from triplicate experiments.

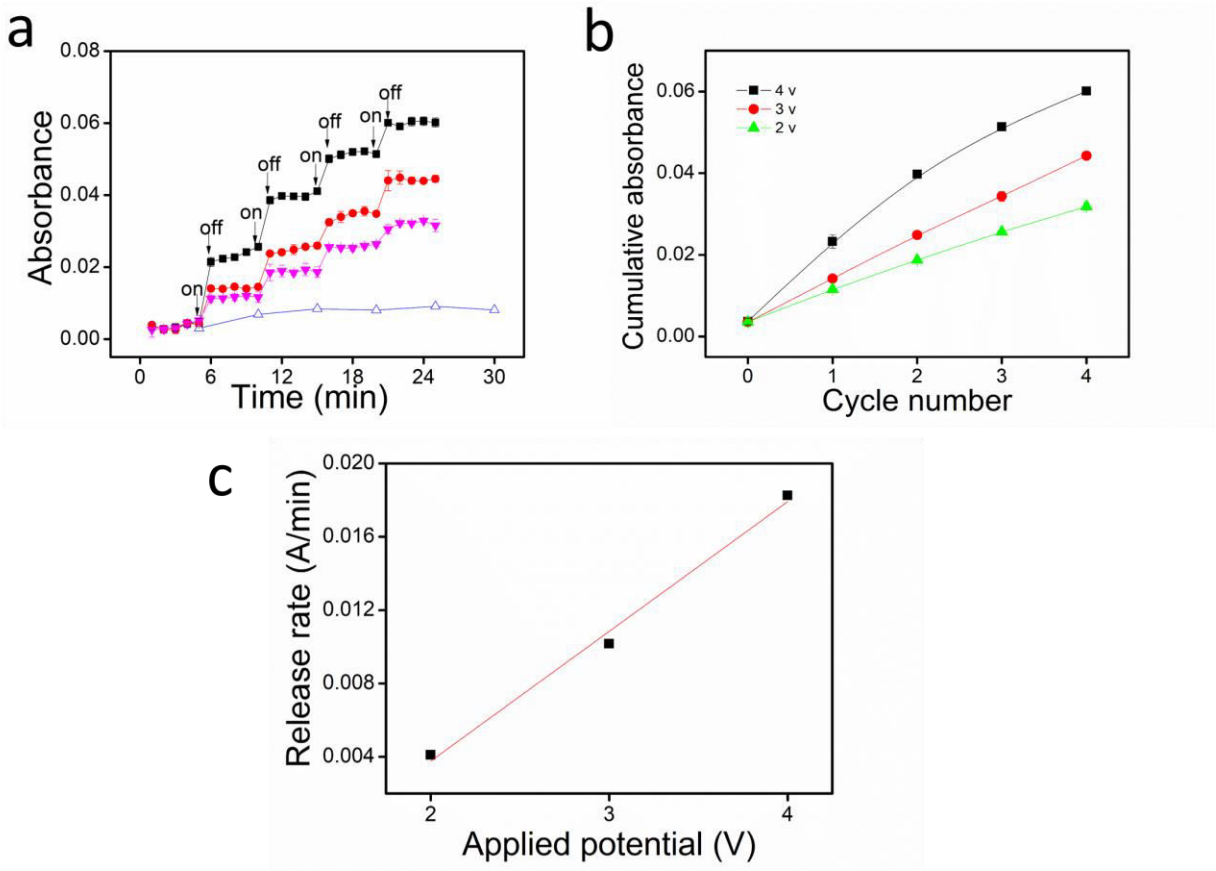

Figure 5. a) CV release profiles for pulsed voltages of (■) 4 V, (●) 3 V, and (▼) 2 V. (△) Release profile for a surface that had no voltage applied. The arrows indicate the times when the voltage was turned on and off. The lines drawn through the data are only to guide the eye. The data points presented here are averages and the error bars are the standard deviations from triplicate experiments; b) Cumulative absorbance as a function of cycle number for the indicated voltages; and c) The release rates for the indicated voltages obtained by determining the initial slopes of the release profiles in (b). The lines in (b) are only for guiding the eye, while the line in (c) was fit by linear regression.

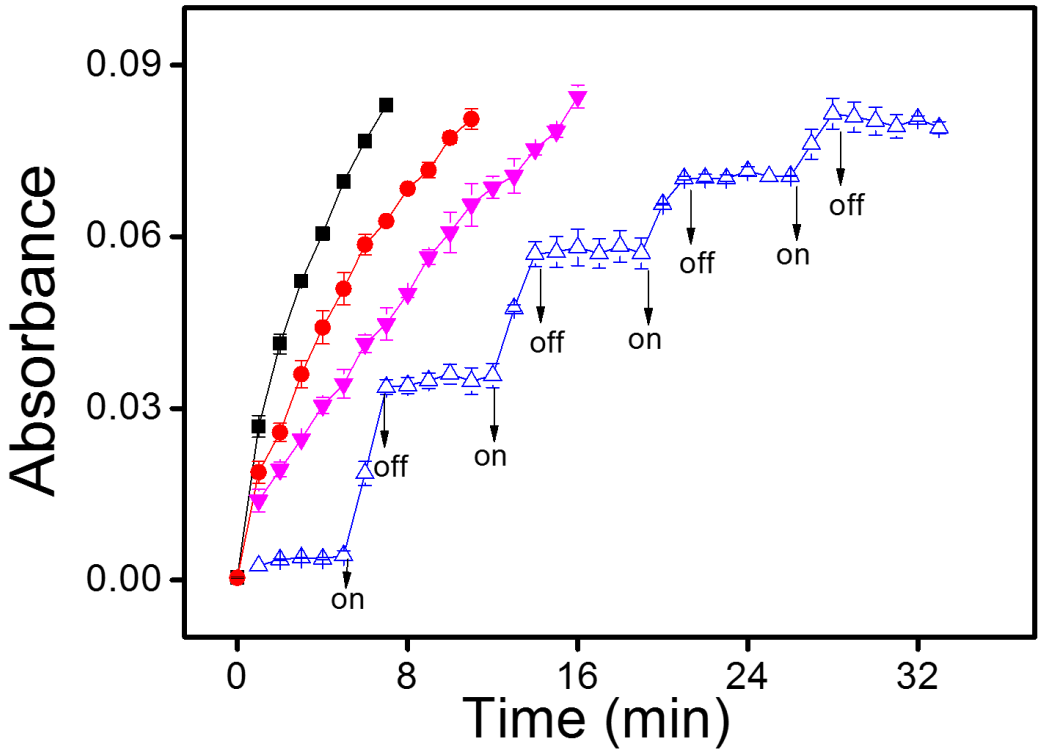

Figure 6. The release profiles for devices that have a continuous voltage of (■) 4 V, (●) 3 V, and (▼) 2 V applied, compared to (△) a device with 4 V applied as pulses. The arrows indicate the times when the voltage was turned on and off. The lines drawn to the data are only for guiding the eye. The data points presented here are averages and the error bars are the standard deviations from triplicate experiments.

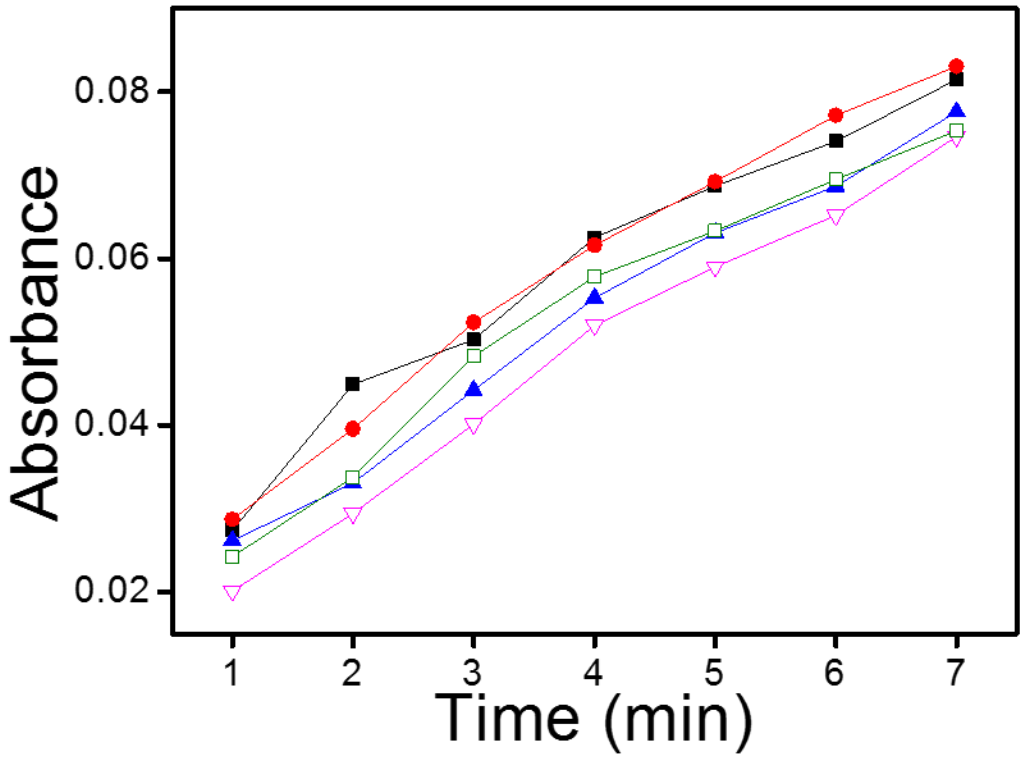

Figure 7. Release profiles for a single device used and reloaded with CV multiple times; (●) first run, (■) second run, (▲) third run, (▽) fourth run, and (□) fifth run. The lines drawn to the data are only for guiding the eye.