Controlled and Triggered Small Molecule Release from a Confined Polymer Film

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ABSTRACT: A device composed of a poly (*N*-isopropylacrylamide)-*co*-acrylic acid (pNIPAm-*co*-AAc) microgel layer sandwiched between two thin Au layers (all on a glass support) was used as a novel platform for controlled and triggered small molecule delivery. Tris (4-(dimethylamino)phenyl)methylium chloride (Crystal Violet, CV), which is positively charged, was loaded into the microgel layer of the device and released in a pH dependent fashion, at a rate that could be controlled by the thickness of the Au layer coating the microgels. Specifically, at pH 6.5 (above the pK_a for AAc) the microgels were negatively charged, promoting the strong interaction between the CV and the microgels, hindering its release from the layer. At pH 3.0 the microgel's AAc groups are protonated making the microgel mostly neutral, allowing CV to be released from the microgel layer at a rate that depends on the thickness of the Au covering the microgels. Specifically, devices with thin Au overlayers on the microgel layer allow CV to be released from the device faster than devices with thick Au overlayers. The ability to tune the

release rate with pH and Au layer thickness is advantageous for developing implantable devices that are capable of releasing small molecule drugs in a triggered and controlled fashion.

INTRODUCTION

Polymer-based materials that are capable of encapsulating small molecules (or drugs) and releasing them in a controlled/triggered manner are well known, pioneered by the work of the Langer group.[1] In the following years a number of functional materials composed of stimuli responsive polymers,[2-4] micro and nanoparticles,[5-7] and porous materials[8-10] have been developed that are capable of releasing a variety of small molecules and macromolecules (e.g., DNA and RNA)[11-14]in a controlled and triggered fashion. Responsive materials have been developed that can respond to external stimuli, for example, temperature,[15] light,[16,17] small molecules,[18] magnetic field,[19] ultrasound[20,21] and electric field.[22,23] Various drug delivery systems, such as liposomes, micelles, polymeric particles and hydrogels have showed great promise for controlled and targeted drug delivery. Among these systems, porous materials are emerging as a new category of drug delivery systems.

Great attention has been focused on the development of porous materials as controlled drug delivery matrices because they can be synthesized to have a stable uniform porous structure with tunable pore sizes and well-defined surface properties. Of particular interest to the work here are porous materials that were used for controlled release of encapsulated species from their pores via regulation of the pore size. Recently, different porous-container materials were used for the controlled release of the small molecules in a reservoir.[8,9,24-31] The Willner group reported that nucleic acid modified mesoporous silica nanoparticles could be used to release a drug in a controlled and triggered fashion.[26] Specifically, they modified the mesoporous silica

nanoparticles with tailored nucleic acids, which defined the pores and pore size. The nucleic acid pores could be cleaved, and thus opened, in the presence of specific ions. This results in the release of the pore-encapsulated substrates. In another example, nitrospiropyran photoisomerizable units were used to modify mesoporous SiO_2 nanoparticles.[27] Photoisomerization of the capping units to the protonated nitromerocyanine opens the channels and releases the encapsulated dye molecules in the nanoparticles. Vasilev and co-workers developed a polymer bilayer-based platform to control the local release of drugs.[31] A polymer-based "sandwich" structure was formed by plasma polymerization followed by embedding of the drug between the two polymer films. The top polymer film was porous, allowing the drug to leak from the bilayer structure at a given rate. They showed that the rate of release could be adjusted by varying the thickness of the top polymer layer. While these systems do show promise, many of the systems are complex and time-consuming to fabricate. Hence, easy to manufacture systems capable of controlling the release of small molecules to a system is needed.

Poly (*N*-isopropylacrylamide) (pNIPAm) is by far the most extensively studied responsive polymer to date.[32-35] It is well known to be thermoresponsive, exhibiting a lower critical solution temperature (LCST) at 32 °C in water. That is, < 32 °C the polymer has favourable interactions with water molecules and exists as a solvated, extended random coil. The polymer-polymer interactions become dominant at > 32 °C, causing the polymer to desolvate and collapse into a dense globular conformation. Furthermore, the transition is fully reversible and can be repeated many times. As the LCST is close to physiological temperature, pNIPAm based materials, such as hydrogels and microgels have been widely exploited in biomedical and biological applications.

Like linear pNIPAm, pNIPAm-based hydrogel particles (microgels) have also been synthesized and are fully water swollen (large diameter) at T < 32 °C, while they are dehydrated (small diameter) at T > 32 °C.[36-39] PNIPAm-based micro and nanogels are most easily synthesized via free radical precipitation polymerization.[40,41] This approach is versatile in terms of the variety of chemical functionality that can be added to the microgels by simply adding functional monomers to the reaction prior to the initiation. Using this approach, pNIPAm-based microgels with a variety of chemical functionalities have been synthesized.[42-44] The most commonly used comonomer is acrylic acid (AAc), which renders the pNIPAm-*co*-AAc microgel pH responsive,[43,45-47]and can also be used to further modify the microgels with other small molecules.[35, 48-50, 52] The pH responsivity is a result of the pK_a of the AAc group. That is, the pK_a for AAc is ~4.25, so when the pH of the environment is < 4.25, the AAc group are protonated and mostly neutral (a slight charge can exists depending on the initiator used), and when the pH > 4.25, the microgels are deprotonated and negatively charged. Therefore, at high pH, the microgels have attractive electrostatic interactions with positively charged species, while they have minimal interactions with positively charged species at low pH.

Recently, our group developed color tunable materials by sandwiching pNIPAm-based microgels between two thin gold (Au) films resulting in the "mirror-dielectric-mirror" configuration of a classic etalon.[45,51-60] The structure of the device is shown in Figure 1. When the device is immersed in water, the microgel layer swells, rendering them thermoresponsive. This allows the thickness of the microgel layer to be tuned by varying the water temperature. Since the color of the devices depends on the dielectric thickness, the color of the devices can be dynamically tuned with temperature, which makes them good sensor devices.[51,59] Using appropriately modified microgels, the etalons can also be made to change color as a function of

pH,[45] and upon exposure to glucose.[52] We also demonstrated that polyelectrolytes can penetrate into the microgel-based layer by entering through the pores in the Au layer (overlayer) covering the microgels, which will in turn change the optical properties of the devices.[55] Finally, we showed that the Au overlayer's pore size can be varied by changing the thickness of the Au overlayer.[57, 58] That is, thick Au has fewer and smaller pores than thin Au. We have been able to exploit this phenomenon for sensing and biosensing applications.[56]

In the present work, we exploit the pH responsivity of pNIPAm-*co*-AAc microgels in etalons, and the pore size control of the Au overlayers, to achieve devices capable of delivering the small molecule tris(4-(dimethylamino)phenyl)methylium chloride (Crystal Violet, CV) to a system. The loading and release mechanism is illustrated Figure 2. CV molecules are positively charged and represented by the blue dots. As mentioned above, an increase in the solution pH to above the pK_a for AAc renders the microgels negatively charged. Thus, at high pH there are strong electrostatic interaction between the microgels and the positively charged CV molecules, which facilitates CV adsorption into the microgel. Reducing the pH of the solution to below the pK_a of AAc renders the AAc groups neutral. Hence, the electrostatic interactions holding the CV into the microgels were destroyed, and the CV could exit the microgel layer. Here, we show that the rate of the release from the etalon depends on solution pH and the thickness of the Au overlayer.

EXPERIMENTAL SECTION

Materials: *N*-isopropylacrylamide (NIPAm) was purchased from TCI (Portland,Oregon) and purified by recrystallization from hexanes (ACS reagentgrade, EMD, Gibbstown, NJ) prior to use. *N,N'*-methylenebisacrylamide (BIS) (99%), acrylic acid (AAc) (99%), and ammonium persufate (APS) (98+%) were obtained from Aldrich (St. Louis, MO) and were used as received.

Sodium chloride was obtained from EMD (Millipore, Billerica, MA), and deionized (DI) water with a resistivity of 18.2 MΩ·cm was used. Cr/Au annealing was done in a Thermolyne muffle furnace from ThermoFisher Scientific (Ottawa, Ontario). Anhydrous ethanol was obtained from Commercial Alcohols (Brampton, Ontario). Sodium hydroxide (NaOH, 99.8%) and hydrochloric acid were purchased from Caledon Chemicals (Georgetown, Ontario) and were used as received. Fisher's finest glass coverslips were 25 × 25 mm and obtained from Fisher Scientific (Ottawa, Ontario). Cr was 99.999% and obtained from ESPI as flakes (Ashland, OR), while Au was 99.99% and obtained from MRCS Canada (Edmonton, AB). Tris(4-(dimethylamino)phenyl)methylium chloride (Crystal Violet, CV) was obtained from Sigma-Aldrich.

Microgel Synthesis: Microgels composed of poly (*N*–isopropylacrylamide)-*co*-acrylic acid (pNIPAm-*co*-AAc) were synthesized via free radical precipitation polymerization as described previously.[53] Briefly, a 3-necked round bottom flask was fitted with a reflux condenser, nitrogen inlet, and temperature probe, and charged with a solution of NIPAm (11.9 mmol) and BIS (0.703 mmol) in 99 mL deionized water, previously filtered through a 0.2 μm filter. The solution was bubbled with N_2 gas and allowed to heat to 70 °C over ~1 hour. AAc (1.43 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 hours under a blanket of nitrogen. 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, 6x. The cleaned microgels were recombined and stored in a brown glass jar.

CV Loaded Etalon Fabrication: CV loaded etalons were fabricated using a previously published protocol[54] with slight modification. The process is shown in Figure 3. To fabricate the Au coated coverslips (etalon underlayer), 2 nm Cr followed by 15 nm of Au was thermally evaporated onto a 25 x 25 mm ethanol rinsed and N_2 gas dried glass coverslip (Fisher's Finest,Ottawa, ON) at a rate of 0.2 Å s^{-1}, and 0.1 Å s^{-1}, respectively (Torr International Inc., thermalevaporation system, Model THEUPG, New Windsor, NY). The Cr/Au substrates were annealed at 250 °C for 3 h (Thermolyne muffle furnace, Ottawa, ON) and cooled to room temperature prior to microgel film deposition. Approximately 10 mL of microgels solution was centrifuged at ~8300 rcf to form apellet at the bottom of a centrifuge tube. The supernatant was removed and discarded, and the pellet was vortexed to loosen and homogenize the particles in the remaining solvent. A 40 μL aliquot of the concentrated microgels was put onto the substrate and then spread toward each edge using the side of a micropipet tip. The substrate was rotated 90°, and the microgel solution was spread again. The spreading and rotation continued until the microgel solution became too viscous to spread due to drying. The microgel solution was allowed to dry completely on the substrate for 2h with the hot plate temperature set to 35 °C. After that, the dry film was rinsed copiously with DI water to remove any excess microgels not bound directly to the Au. The film was then placed into a DI water bath and allowed to incubate overnight on a hot plate set to ~30 °C. 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 put into 20 mL of a CV solution (4 mg/mL, pH of 6.5) overnight. Excess CV was rinsed off the substrate with pH 6.5 solution (to not disturb the microgel-CV interaction) and incubated in pH 6.5 solution overnight followed by drying with N_2 gas. Another Au overlayer (2 nm Cr for adhesion, followed by

deposition of different thicknesses of Au overlayers) was evaporated onto the CV loaded microgel layer. Since we were interested in understanding how the Au overlayer thickness affected the rate of CV release from the etalon, we sealed the etalon's edges with clear nail polish.

CV Release: A Petri dish filled with 20 mL of pH solution was placed on a hot plate, and the solution temperature maintained at 25 ^{o}C. In our experiments, we use two pH values, 3.0 and 6.5. The solution in the Petri dish was stirred continuously at 260 RPM using a magnetic stir bar. The solution was flowed through a cuvette in an Agilent 8453 UV-Vis spectrophotometer, equipped with an 89090A temperature controller and Peltier heating device, via a peristaltic pump. The CV loaded etalon was added to the Petri dish, and a timer started. The absorbance spectrum from the solution was collected every 30 s. The flow rate of the solution was measured before and after each experiment, and was used (along with the time measurements) to calculate a volume.

RESULTS AND DISCUSSION

Microgel-based etalons have been reported by our group as an optical device that can be used to sense ions,[51] glucose,[52] or biomolecules.[56,60] It can also be used as a platform to study the penetration of macromolecules into confined spaces.[55] Here, we show that the structure can be used for controlled and triggered small molecule (or "drug") release to a system. To accomplish this, the pNIPAm-*co*-AAc microgel-based etalon device was fabricated using the protocol shown schematically in Figure 3. Initially, 2 nm Cr and 15 nm Au was thermally evaporated on the glass substrate, followed by annealing and deposition of the microgel layer. The microgel layer was loaded with CV as detailed above; CV was used as a model drug. CV is hydrophilic, positively charged, and has an absorbance maximum at ~590 nm, which makes it easy to detect

spectrophotometrically and the purple color of CV solution makes it easily visible, see Supporting Information.

Next, Au was deposited on the CV loaded microgel layer to form the top Au overlayer of the etalon. Again, the edges of the etalon were sealed with clear nail polish to prevent CV leakage out of the sides, and to ensure that the CV only exited the device through the Au overlayer. The device (in this example with a 500 nm overlayer) was added to a Petri dish containing pH 6.5 solution, and the solution's absorbance spectrum collected every 30 s. The UV-Vis spectra are shown in Figure 4. The absorbance value at 590 nm was used to quantify the amount of CV in solution after releasing. As can be seen in Figure 4(a), in pH 6.5 solution the increase was quite minimal, this was in contrast to a CV-loaded etalon exposed to pH 3.0 solution, which is shown in Figure 4(b). From the data, it is clear that for a given Au overlayer thickness, we are able to control the release rate with pH by modulating the CV-microgel interaction. It is worth noting here that the spectrum of CV was unaffected by the Au deposition process.

In order to evaluate how the rate of CV release from the etalon was affected by Au overlayer thickness, we constructed CV-loaded etalons with four overlayer thicknesses 50, 200, 500 and 700 nm. The release profiles for the CV-loaded etalons with different Au overlayer thicknesses were evaluated at for the etalon exposed to pH 6.5 and then pH 3.0 solutions. For these experiments we simply monitored the absorbance at 590 nm over time. Figure 5(a) shows CV molecule release from etalons in pH 6.5 solution. The data show that at this pH, the release was slow due to the favourable electrostatic interactions between the CV and the microgels, as discussed above. Figure 5(b) shows CV release from the etalons at pH 3.0, and clearly shows that the Au overlayer thickness plays a major role in controlling the release rate. It is important to mention here that volume, instead of time, was used as the x-axis since the flow rate was variable

from sample to sample. The 50 nm Au overlayer sample released the CV the fastest, while the 700 nm Au overlayer released CV the slowest. The rate of CV released appears to scale with Au overlayer thickness. In previous studies, we have shown that the average pore size decreases with increasing Au overlayer thickness.[57] So we attribute the slower release kinetics as a function of increasing Au overlayer thickness to the decrease in Au pore size. It is interesting to note that the amount of CV released from each film varies with Au overlayer thickness. While this is not well understood, we attribute this to the thicker Au overlayers trapping the CV in a state in which it is not able to be released, e.g., trapped under a large Au section with no pores nearby. For controls, we showed that ambient light and pH had no effect on the CV spectrum, as shown in Supporting Information. Finally, we show that the thermoresponsive nature of the pNIPAm-based microgels can be used to accelerate the release of the CV from the etalon at a given Au overlayer thickness. As can be seen in Figure 6, when an etalon with a 700 nm Au overlayer is initially immersed in pH 3.0 solution at 25 ^{o}C the release rate is much slower than when the solution temperature is increased to ~47 ^{o}C, showing that the collapse of the microgels in the etalon can accelerate the release rate.

We also point out here that the CV release rates for microgels in etalons are much faster than the same microgels in solution, see Supporting Information. We hypothesize that this is a result of the microgels being in a monolayer sandwiched between the two Au layers. The sandwiching process results in microgels that are approximately half their solution diameter, hence then have a smaller distance to diffuse into the solution, leading to an increased release rate compared to the larger microgels in solution. We also point out here that the microgels in solution were slightly aggregated after CV addition for microgel loading. This further increases the effective distance CV needs to travel to get out of the microgels and into the solution. Although, the

kinetics are so much different for microgels in etalons versus in solution that there must be another process forcing the CV out of the microgel layer of the etalon. This may be a result of the microgel layer contracting when the solution pH is lowered to pH 3.0 due to the charge neutralization in the microgel layer. It is well known that pNIPAm-*co*-AAc microgels contract when AAc is neutralized when going from pH 6.5 to pH 3.0. This contraction could mechanically push the CV out of the microgel layer leading to an increased release rate.

It has been clearly demonstrated that the microgel-based etalon device could be used to control the rate of release of a small molecule "drug" to a system. The ability to control the amount of the small molecule released in a given amount of time is also of importance to design on demand drug delivery systems. Figure 7 clearly shows that CV can be released from the etalons on demand, and the release halted by simply changing the pH. To accomplish this, we first immersed the CV-loaded etalon (500 nm Au overlayer) in pH 6.5 solution and monitored the release for 15 min. Following this period, we lowered the solution to pH 3.0 by adding hydrochloric acid, and after few minutes monitoring, the pH was increased to 6.5 again by adding sodium hydroxide (0.1 M). The solution pH was continuously monitored using a pH meter. This process was repeated, and as can be seen in the figure, the on-off process can be repeated many times.

CONCLUSIONS

In this article, we developed a controlled and triggered "drug" delivery system utilizing pNIPAm-*co*-AAc microgel-based etalons. The drug release can be triggered by varying the solution pH, with the release rate controlled by the thickness of the Au overlayer covering the microgels. Furthermore, we showed that the model drug could be released in a triggered fashion,

turning on and off as a function of solution pH. In future, these devices will be used to release large macromolecular "drugs" from the confined microgel layers.

FIGURES:

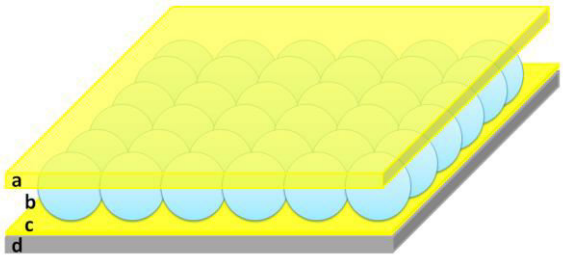

Figure 1. Structure of a pNIPAm microgel-based etalon. (a) and (c) are 15 nm Au layers (with 2 nm Cr adhesion layer) sandwiching (b) a microgel layer all on a (d) glass substrate.

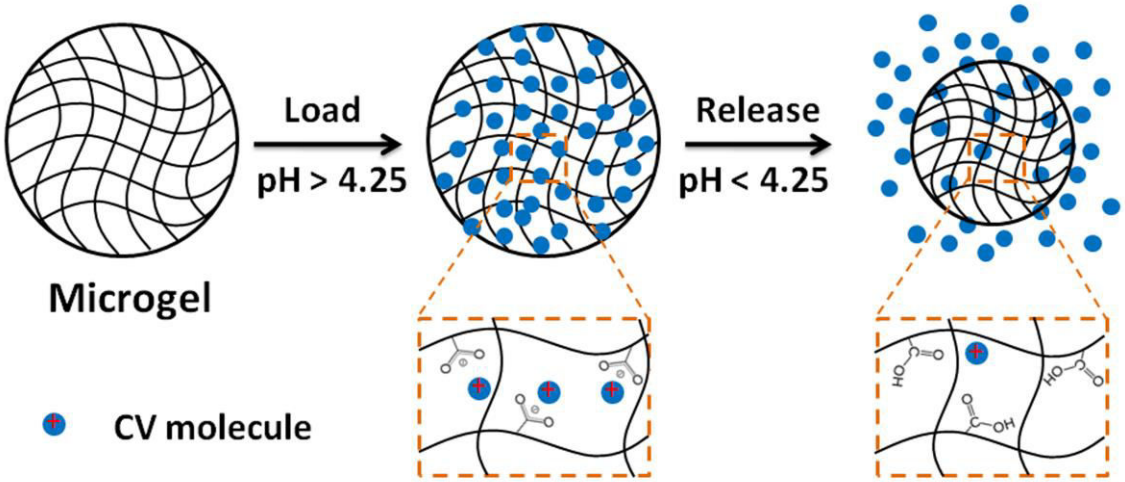

Figure 2. The loading and release mechanism of CV molecules into and out of pNIPAm-*co*-AAc microgels.

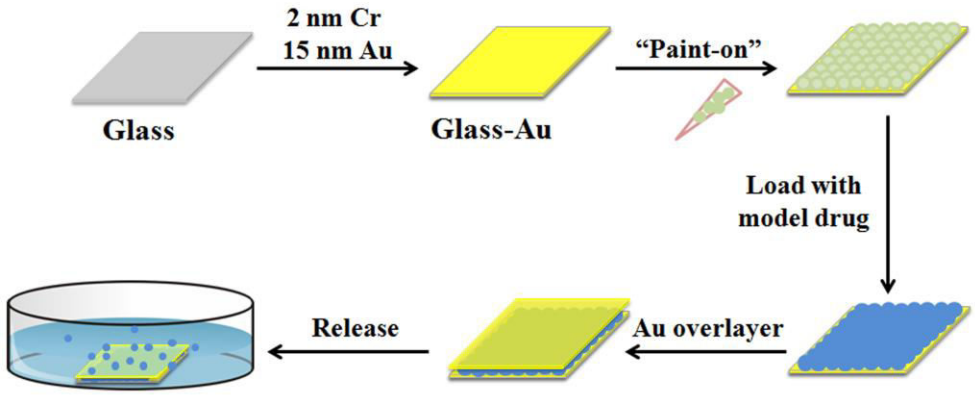

Figure 3. Schematic of the fabrication of CV (drug) loaded etalons and the release process.

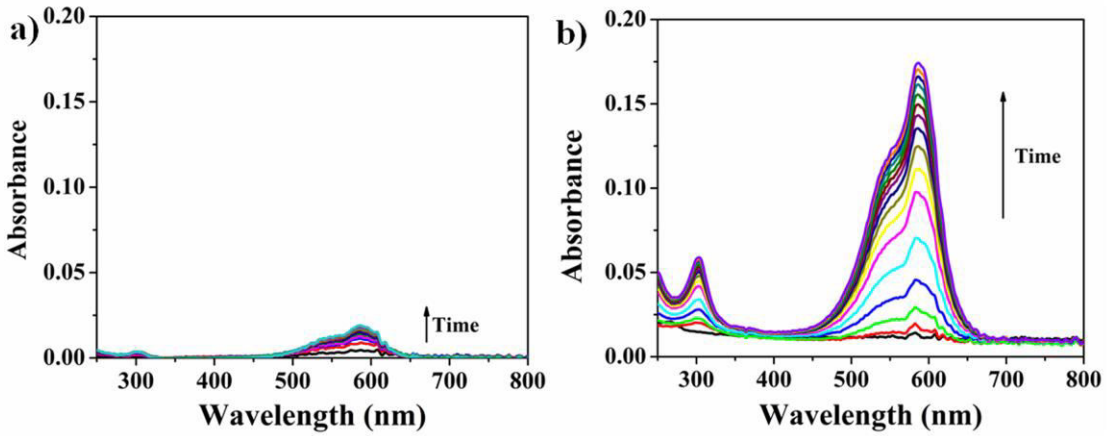

Figure 4. Release of CV over time, monitored via UV-Vis spectrophotometer, in (a) pH 6.5 and (b) pH 3.0 solutions. The Au overlayer thickness of this sample was 500 nm. The maximum absorbance is at 590 nm and the absorbance increase with time. The spectra were obtained every 30 sec, and the total release time was 2 h; here we show spectra for the first 10 min of release.

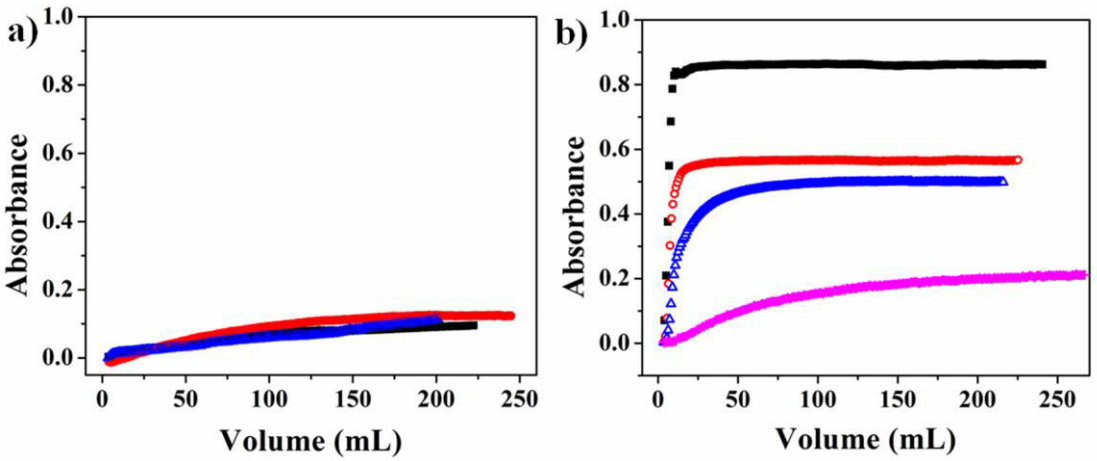

Figure 5. The release profiles for the microgel-based etalon devices in (a) pH 6.5 and (b) pH 3.0 solutions. The Au overlayer thicknesses were (■) 50 nm, (O) 200 nm, (△) 500 nm, and (+) 700 nm. In all cases, the total release times were 2 h. Since the flow rates were variable from experiment to experiment, the total volumes are slightly different, but allow for direct comparisons of the data with flow rate irrelevant.

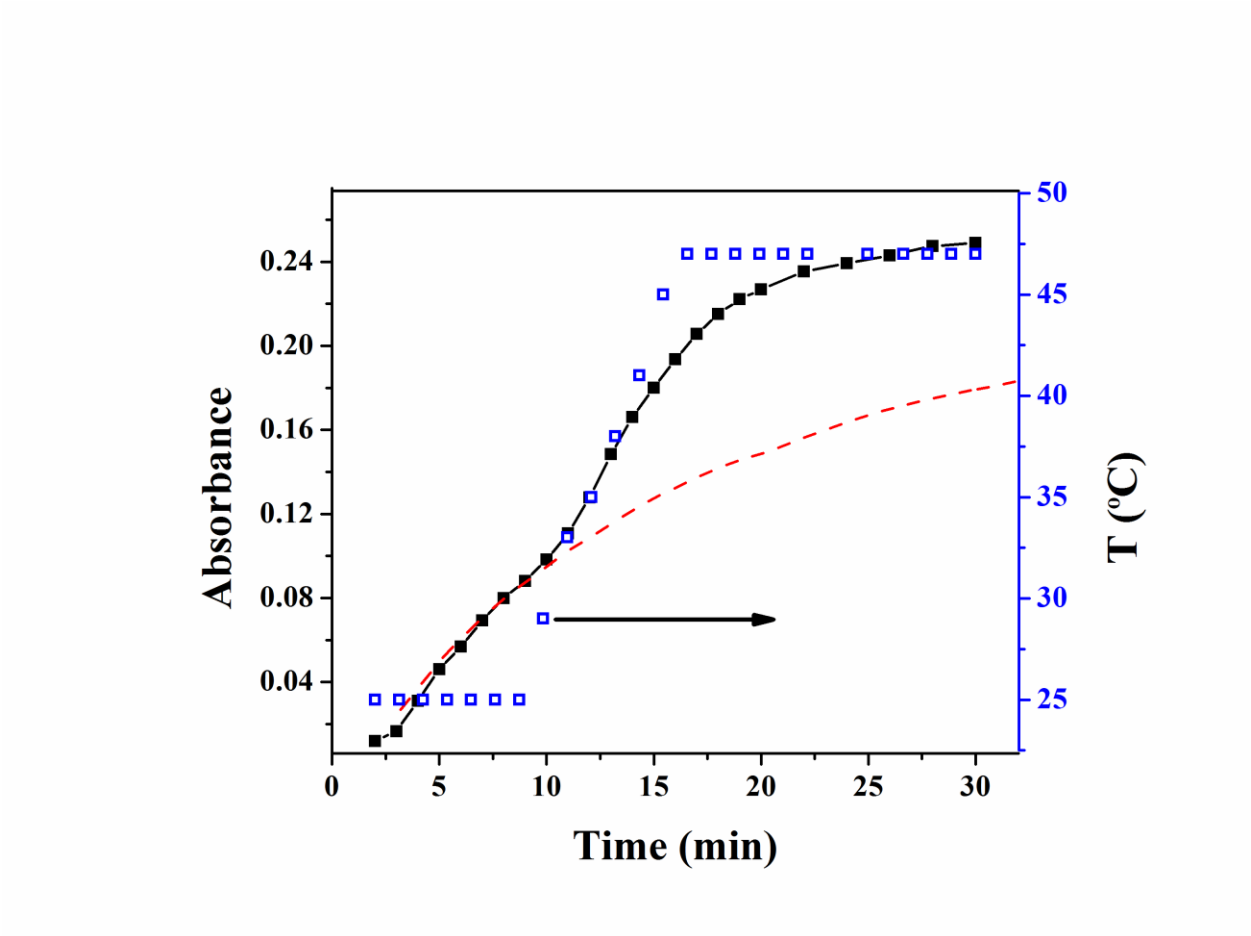

Figure 6. A CV loaded etalon with a 700 nm Au overlayer was immersed in pH 3.0 solution at (□) 25 ^{o}C while the (■) CV release profile was collected. At 9 min, the solution temperature was increased to ~47 ^{o}C while the release profile was continuously monitored. As can be seen, the release rate dramatically increased when the solution temperature reached ~ 33 ^{o}C (>LCST for pNIPAm). The red dashed curve shows the predicted release profile if the solution temperature was held continuously at 25 ^{o}C clearly illustrating the increased release rate.

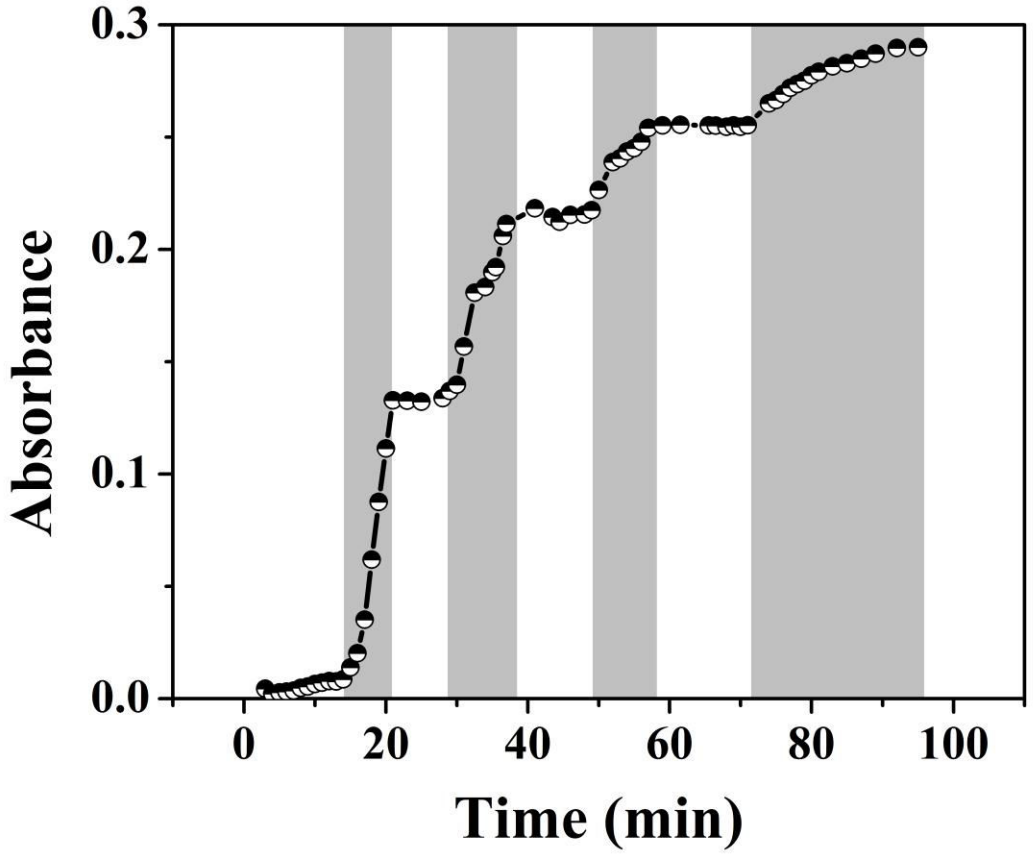

Figure 7. pH triggered release profile from an etalon with 500 nm Au overlayer. The dark regions represent where the solution pH was changed to 3.0, while the white regions are where the solution pH was 6.5. As mentioned, the solution pH was varied by adding either HCl or NaOH.

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ASSOCIATED CONTENT

Supporting Information. Images of samples before and after CV loading; relationship between Au overlayer thickness and released amount and release rate; control experiments for CV at different pHs and after light exposure; CV molecules release profile from poly (NIPAm-*co*-AAc) microgels in solution. Control experiment showing that nail polish can block CV from entering solution from the etalon and the effect of temperature on CV. This material is available free of charge via the Internet at http://pubs.acs.org.

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