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Evidence of Hydrophobic Interactions Controlling Mobile Ions Release from Smart Hydrogels

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A water soluble cationic metal complex (tris(2,2′-bipyridine)ruthenium(II)) can be loaded into hydrogels containing acrylamide and/or acrylic acid units. The cationic complex is retained in polymer containing acrylic acid units at high pH and released at low pH. This is likely due to electrostatic interactions of the cation with the carboxylate anions, present at high pH, which are converted into neutral carboxylic acid at low pH, releasing the metal complex. Since the gel contract at low pH, the water soluble cation is also released with the water expelled from the gel. However, a strong retention of the cation inside the gels is observed when acrylamide units are present. A possible explanation is a hydrophobic interaction of the large metal complex with the polyacrylamide network. Using the counteracting electrostatic and hydrophobic interactions of probe molecules with smart hydrogel matrixes it is possible to tune the pH of maximum release away from the pKa of the ionizable group.

Keywords Cationic complex; hydrogels; hydrophobic interaction; metal complex; polyacrylamide network

Introduction

Hydrogels are one promising types of polymer materials which do not dissolve in water but swell considerably in aqueous medium [1]. Smart hydrogels are stimuli responsive materials which suffer a phase transition, with volume change, in response to changing environmental conditions such as temperature, pH, solvent composition or electrical stimuli [2]. These materials have been attracting much attention in medical and mechanical engineering fields [3–5]. Also, hydrogels have been used in the medical device industry as contact lenses [6], artificial muscles [7], controlled cell adhesion [8], and sensors [9]. One of the most thoroughly studied smart hydrogels is poly(acrylic acid) (pAA) [10]. The carboxylate group in the polymer backbone can be easily converted into carboxylic acids at low pH (pKa 4.3) [11]. The neutralization is accompanied by a significant decrease of the hydrogel volume. Besides the elimination of ion-dipole interactions between water and carboxylate

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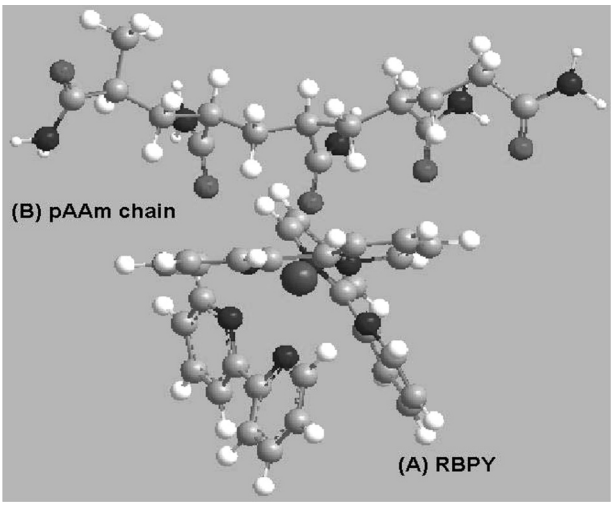
groups, the main factor involves the expulsion of mobile counterions, which are not longer needed to balance the fixed negative charges inside the gel [10]. When the mobile counterions are present inside the gel, a large amount of water is present to maintain the concentration, which determines the chemical potential, low. The water is expelled from the gel together with the counterions upon neutralization of the carboxylate groups. If water soluble mobile cations are present inside the gel, they should be expelled at low pH. Such behaviour has prompted the use of polyacrylic based hydrogels in drug release devices, where cationic drugs can be released in low pH media, such as the stomach or higher intestine [12]. In such applications it is necessary to improve the mechanical properties of pAA and/or lower the amount of volume contraction. An easy way to do that involves the copolymerization of acrylic acid with another water soluble monomer which is not affected by pH, such as acrylamide. In the present communication it is shown that acrylamide units in such copolymers are not indifferent and could have a strong effect in the release of retained molecules.

Experimental

All reagents are of analytical quality. The metal complex (tris(2,2′-bipyridine) ruthenium(II) chloride, $Ru(bpy)_3Cl_2$) (Aldrich) (Scheme 1A) was used as received. The UV-vis spectra were measured in optical glass (Helma) 1 cm cells using a HP-8452A diode array spectrometer.

Polymerization

Monomer (acrylamide and/or acrylic acid, total concentration 0.5 M)) and cross-linker (N,N′-methylenebisacrylamide, 10 mM) were dissolved in distilled water. The free radical polymerization of the hydrogels was carried out in a glass tube at room temperature (22°C) for 3 h, using ammonium persulfate (0.001 gr/ml) and



Scheme 1. MMF94 minimized Chemical structures of: (A) a the metal complex (RBPY), (B) a short section of pAAM chain.

N,N,N′,N′-Tetramethylethylenediamine (10 µl/ml) as redox initiator and activator, respectively. After the polymerization, the hydrogels were immersed in running distilled water at room temperature for 48 h. The mean number of monomer units between crosslinks is similar for.

Swelling Measurements

The swelling ratio was measured in various buffer solutions. To do that, preweighted dry hydrogels samples were immersed in solutions with various pHs until they swelled to equilibrium. It was confirmed that 10 h equilibration was enough to reach the equilibrium swelling of samples. After excessive water was removed with filter paper, the fully swollen gel is weighted and the swelling percentage calculated using Eq. (1)

$$\%\,swelling = 100 * \left(\frac{Ws - Wd}{Wd}\right) \tag{1}$$

where *Ws* represents the weight of the swollen state of the sample and *Wd* is the weight of dry sample. The swelling experiments were repeated five times until there was no further weight increase.

RBPY Release

The amount of metal complex tris(2,2′-bipyridil) ruthenium(II) (RBPY) released from the gel is measured by uv-visible spectrophotometry in the solution outside the gel. Preweighted dry hydrogels samples were immersed in RBPY solutions with various pH values until they swelled to. The data of initial absorption ($Abs(t_0)$) of RBPY solution and after 72 hs Abs(t) were registered. Percentage of retention of RBPY inside of gel is calculated as the difference between Abs(t) and $Abs(t_0)$ of RBPY solution, relative to initial absorbance ($Abs(t_0)$) per gram of hydrogel (Eq. (2)).

$$\%retention = 100 * \left[1 - \left(\frac{Abs(t) - Abs(t_0)}{Abs(t_0) * Wd}\right)\right] \tag{2}$$

The spectra of RBPY solutions freshly prepared and those released from the gels are identical indicating that the complex is released as one unit and the polymer matrix does not exchange the metal with the complex.

Contact Angle

A computer controlled microscope Intel QX3 was used for measurement of contact angle by setting flat polymer pieces on a manually controlled tilt table, illuminating from behind with a white led source and recording, with the microscope in horizontal position, the shape of water drops (3 µl) standing still on the surface using a 60X objective. The pictures were analyzed using "Drop Analysis" software.*

*Biomedical Imaging Group, download algoritm. http://bigwww.epfl.ch/demo/dropanalysis/

Molecular Simulation

The chemical structures were drawn using ChemBioDraw Ultra (11.0) and minimized using the Merck Molecular Field 94 (MMF94) routine available in ChemsBio3D Ultra (11.0), using a gradient norm of 0.01.

Results and Discussion

In Figure 1 are shown the swelling percentage of different hydrogels at different pH.

As it can be seen, poly(acrylic acid) (pAA) based hydrogels swell more significantly at basic (10) than at neutral (7) or acid pH (4). This is likely due to the presence of negative charges, accompanied by mobile counterions, inside the gel at pH 7 or 10. On the other hand, the gel of polyacrylamide (pAAm) shows a small swelling, irrespective of the pH since there are not ionizable groups present. The difference of swelling percentage suggests that, even pAA gels containing neutral –COOH groups are more hydrophylic than pAAm gels. A hydrogel based on a copolymer showed the same behaviour than pAA but with lower swelling percentage due to the presence of acrylamide units. The results agree with reported swelling data of similar hydrogels [13]. It is noteworthy that a copolymer with a higher amount or acrylamide than acrylic acid (60/40) was used to highlight the effect of acrylamide units.

In Figure 2 are shown the percentage of RBPY retained inside the hydrogels when a piece was swelled in a solution of the complex at different pH. As expected, pAA gels retain a significant amount of cation at high pH, when the matrix bars negative charges. When the pH is lowered, therefore the matrix is neutral, the amount of RBPY retained diminishes. On the other hand, pAAm gels show a similar behaviour irrespective of the pH. This is reasonable as the gel does not contain groups ionizable in the pH range 0–14. More that 80% of the RBPY is retained inside the gel when it is contacted with an excess of solution. It is likely that the

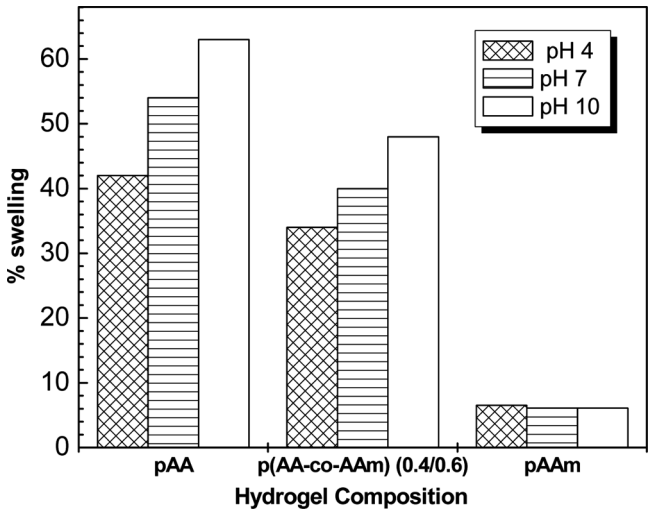


Figure 1. Swelling of hydrogels in solutions of different pH.

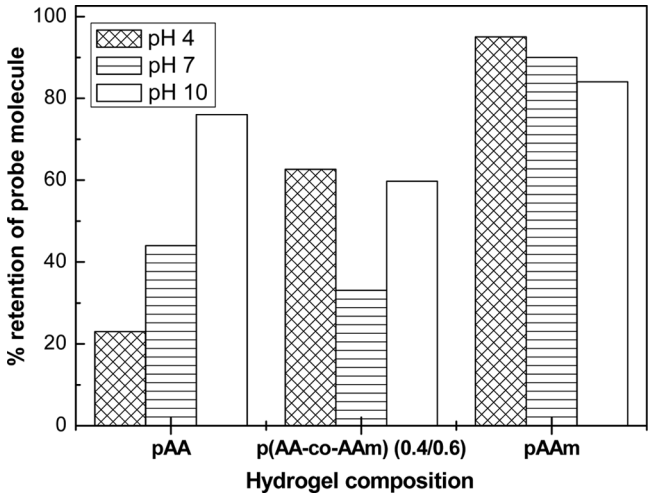
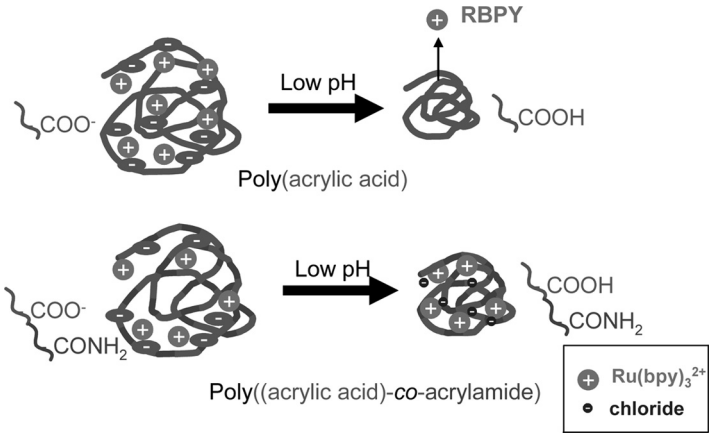


Figure 2. Percentual retention of a probe molecule, inside the hydrogels, when the gel is immersed in solutions of different pH.

large organic part of the complex have hydrophobic interactions with the acrylamide matrix [14]. It is noteworthy that the complex is as large as 3–4 pAAm monomer units (Scheme 1), making the dispersion interactions important.

The copolymer shows an intermediate behaviour. The hydrogel has different retention ratios when the pH is changed. Additionally, a significant amount of RBPY is retained inside the gel at low pH (when the carboxylic unit is not ionized). The combination of electrostatic and hydrophobic interactions makes that the retention of RBPY have a minimum at pH 7. Therefore, changing the ratio of acrylamide to acrylic acid monomer units it is possible to tune the opposite effect and produce the maximum cation release at a pH quite different from the pKa value of the ionisable units (4.3 in this case). Hydrogen bonding interactions between acrylamide and acrylic acid units could also play a role [15]. Obviously,



Scheme 2. Proposed mechanism of RBPY release from copolymer hydrogels.

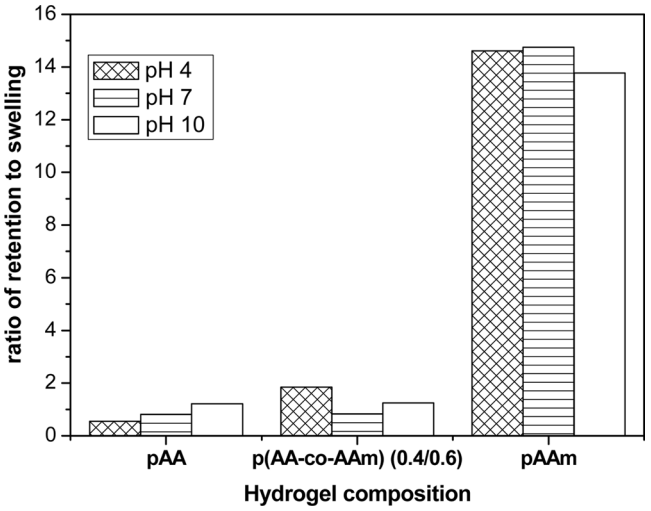


Figure 3. Ratio of the probe molecule retention and the swelling capacity.

the interactions will depend on the probe molecule and different behaviours could be found depending on the charge and hydrophobicity of the probe molecule. The proposed mechanism is summarized in Scheme 2.

While mobile counterions are present inside the RBPY loaded gel at low pH, they seem to exert small influence on the osmotic pressure. Taking into consideration that hydrogel swelling allows more space to retain the cations, the ratio of retention capacity and swelling percentage was plotted (Fig. 3). As it can be seen, the effect is clearer in terms of volume. The pAAm hydrogel can retain 15 times more RBPY than pAA.

Measuremnents of contact angle of water drops on the hydrogels (Fig. 4) confirms that introduction of acrylic acid increases the hydrophilicity since the contact angle changes from ca. 93 degrees in poly(acrylamide) to ca. 78 degrees in the copolymer (0.4/0.6). The contact angle of poly(acrylic acid) is too low to be measured.

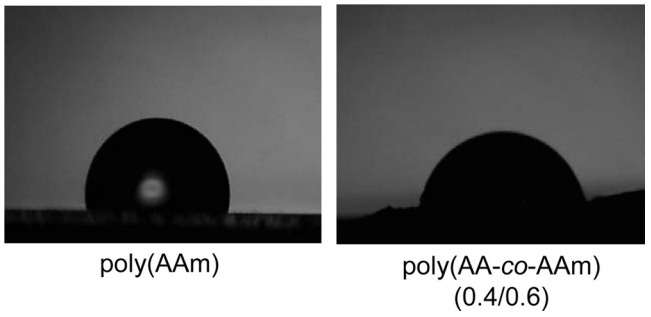


Figure 4. Contact angle of water drops on poly(acrylamide) (left) and poly(Acrylamide-co-Acrylic Acid) (0.4/0.6) (right).

Conclusions

The retention of a large multicharged metal complex depends strongly on the hydrogel matrix composition. Hydrogels containing only acrylamide units can retain ca 15 times more RBPY per unit volume. On the other hand, changing the copolymer composition allows producing smart hydrogels which release a probe molecule at a given pH, which is different from the pKa of the ionisable group. These results suggest that drug release cannot be directly predicted from the relationship between the charge of the mobile ion and the polymer matrix but have to be measured experimentally for each hydrogel/drug pair. Moreover, the almost irreversible retention of a fluorescent cation inside an hydrogel matrix allows us to build a device which memorizes an environment change (pH, temperature, etc.) by combination of the polyacrylamide hydrogel with a smart hydrogel.

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