# Synthesis and Swelling Behaviors of Biodegradable pH-Sensitive Hydrogels Composed of Poly(Acrylic Acid) and Poly(L-Glutamic Acid)

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**Statement of Purpose:** Hydrogels have been used extensively in the development of the smart drug delivery systems. Smart hydrogels are those that can respond to the changes of the environmental conditions, such as temperature, pH, ion strength, pressure, etc[1,2]. Among the environmental stimuli, pH is a widely investigated chemical stimulus, for it can be used as a trigger of controlled release in the gastric-intestinal (GI) track. Here we report a biodegradable pH sensitive hydrogel composed of poly(acrylic acid) (PAA) and poly(L-glutamic acid) (PGA). PGA is both biodegradable and pH-sensitive, with the $pK_a$ at 4.51. The hydrogel showed different swelling ratios (SR) in buffers with different pH values, indicating a pH-sensitivity. The influence of the PGA content on the SR of the hydrogel was also characterized.

**Methods:** PGA was synthesized as reported by our group before [3]. Firstly, poly (γ-benzyl-L-glutamate) (PBLG) was prepared by the ring opening polymerization (ROP) of BLG-NCA. After polymerization, hydrobromide was used to remove the γ-benzyl group. Then 2-hydroxyethyl methacrylate was conjugated to the PGA, with the amount 15 mol % with respect to carboxyl group of PGA, using EDC•HCl and DMAP as the coupling agent and catalyst, respectively. PGA-HEMA and AA (total amount of 500 mg) at different weight ratios were dissolved in phosphate buffer (pH=7.4, 0.1M). APS was used as the free radical initiator. Gelation was carried out at 60℃ for 24h. Five samples were synthesized and characterized. To measure the pH-dependent swelling behaviors, samples were immersed in buffers at different pH values for two days. Samples were weighed at certain time. The SR was calculated based on the equation: $SR=(W_t-W_0)/W_0$, where $W_t$ and $W_0$ are the weights of the swollen gels and dried samples, respectively. All the experiments were carried out in triplicate, and the average values were reported.

**Results:** Samples with different composites were denoted as 3/7, 4/6, 5/5, 6/4 and 7/3, respectively, which represented the PGA/PAA weight ratios of the hydrogels. The swelling behaviors of gels measured at different pH are shown in Figure 1. As expected, the hydrogels had a lower swelling ratio in an acidic medium because of the deprotonation of both PAA and PGA. For example, the swelling ratios of all hydrogels were less than 10 at pH 1.2. While in the basic medium (pH 8.3), the highest swelling ratios were 5 to 10 times higher than that in the acidic medium. The SR increased sharply when the pH was increased from 4, which was consistent to the $pK_a$ of PAA and PGA. Comparing the swelling behaviors of different samples in neutral pH, we found an interesting phenomenon. The sample with the lowest SR was the one composed of 50% PGA and 50% PAA, of which the SR was only about 30. In contrast, with either more PGA or more PAA, the SR got higher. The reasons may be as follows: on one hand, the molecular weight of PGA is high, leading to the reduction of the reactivity of the HEMA groups linked to the PGA backbone with AA. With the increase in the PGA content, the crosslinking density decreased. On the other hand, PAA is much more hydrophilic than PGA, so the hydrogel with higher PAA content is more hydrophilic. Both lower crosslinking density and better hydrophilicity will lead to a higher SR. The samples reached swelling balance within 2 hours, so the drugs loaded may be released quickly in neutral and basic environment. The hydrogels were degraded in 24 hours with the presence of Proteinese K.

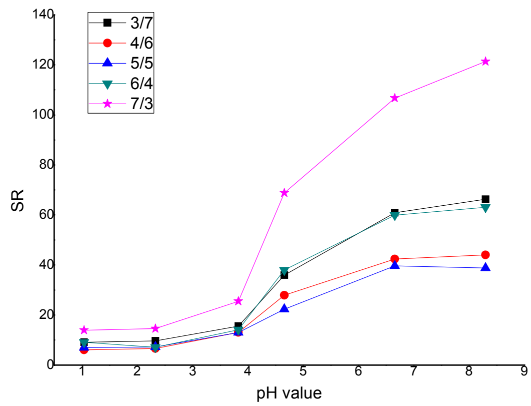


Figure 1. Swelling ratios of hydrogels in buffers at different pH values

**Conclusions:** A novel of pH-sensitive hydrogel was synthesized. The hydrogel underwent a hydrophobic-hydrophilic transition when the pH value of the environment rose from 1 to 8. The hydrogels showed pH-dependent swelling behaviors. The composition of the hydrogels also influenced the swelling ratios. The hydrogels reached swelling balance in water within 2 hours. So we may expect that if drug is loaded into the gels, it can be protected in the stomach, where the pH is less than 2, and be quickly released in the small intestine, with both a swift swelling and degradation of the PGA part. The novel pH-sensitive hydrogels may have potential applications for oral delivery of protein drugs.

**References:**

[1] Hui-Jeong Gwon, Youn-Mook Lim, *et al.* Biotechnology And Bioprocess Engineering, 2009, 15, 392-399
[2] Bajpai, AK; Shukla, SK; Bhanu, S, *et al*, Progress In Polymer Science, 2008, 33, 1088-1118
[3] He CL, Zhao CW, Guo XH, *et al*, Journal of Polymer Science Part A: Polymer Chemistry, 2008,46,4140-4150