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Swelling properties of aspartic acid-based hydrogels

Tamás Gyenes, Viktória Torma, Miklós Zrínyi *

Department of Physical Chemistry, Budapest University of Technology and Economics, HAS-BME Laboratory of Soft Matters, H-1521 Budapest, Hungary

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Abstract

Chemically crosslinked poly(aspartic acid) (PASP) gels were prepared by the hydrolysis of polysuccinimide (PSI). This latter was prepared by thermal polycondensation of aspartic acid. The PSI chains were crosslinked by 1,4-diaminobutane. The consecutive reactions of hydrolysis and swelling kinetics of PSI- and PASP-based gels were studied at different pH values. Two distinct swelling mechanisms were proposed. The cooperative diffusion coefficient has been found to be three orders of magnitude higher in pH 14 solution than at pH 8.

Keywords: Poly(aspartic acid); Gel; Swelling kinetics

1. Introduction

The importance of biodegradable polymers and hydrogel materials is being increasingly recognized, and extensive studies have been conducted on their uses in various biomedical applications [1–3]. Hydrogels based on both natural and synthetic polymers have continued to be of interest for encapsulation of drugs, and most recently, such hydrogels have become especially attractive to the new field of "tissue engineering" as matrices for repairing and regenerating a wide variety of biological tissues and organs [4–6].

Poly(amino acid)s connected by peptide bonds are known to be biocompatible and biodegradable. The 21 proteinogenic amino acids in the peptide chain provide practically infinite variability of the polymers. The preparation of polymer gels with high swelling ability as well as good mechanical properties requires poly(amino acid) network chains with average polymerization degree exceeding 500. Therefore, amino acid-based hydrogels are usually synthesized by crosslinking biological or natural polypeptides, e.g. gelatine or albumin [7,8]. An alternative approach for the preparation of high-molecular-mass artificial polyamides is the thermal polycondensation of amino acids [1,9].

Poly(aspartic acid) (PASP) is a promising water-soluble and biodegradable polymer that can be prepared by hydrolysis of polysuccinimide (PSI) [10–12]. The precursor polymer PSI is prepared by the thermal polycondensation of aspartic acid [12,13], similarly to the most common artificial polypeptide, the nylon. When crosslinked and hydrolyzed, PASP has a high water absorbency, which is pH- and electrolyte-sensitive in water or body fluids [9,14]. It is worth mentioning that PASP is currently in commercial use as a dispersing agent [15].

PASP-based gels were studied by Giammona et al. [13] and by Kim and coworkers [9,15]. It is now firmly established that the imide rings open upon alkaline hydrolysis of PSI, forming α- or β-carboxylate groups on the polymer backbone from the activated, non-equivalent carbonyl groups (see Scheme 1). Similar nucleophil reaction of PSI with amines results in formation of imide groups. As a consequence PSI can be crosslinked by diamines to yield gels.

The cooperative diffusion constants of the polymer backbone in PSI- and PASP-based hydrogels were determined. The kinetics of swelling and shrinking of neutral gels was investigated by several research groups [16–21]. In this work, we study the swelling kinetics of a hydrophobic gel (PSI). During swelling in alkaline solution the hydrophobic PSI gel is converted to hydrophilic PASP gel. Consecutive mechanisms of swelling and hydrolysis can be proposed for this process. Our work tries to

* Corresponding author at: Department of Physical Chemistry and Material Science, Budapest University of Technology and Economics, Hungary. Tel.: +36 14633229; fax: +36 14633767.
E-mail addresses: tgyenes@mail.bme.hu (T. Gyenes), vtorma@mail.bme.hu (V. Torma), zrinyi@mail.bme.hu (M. Zrínyi).

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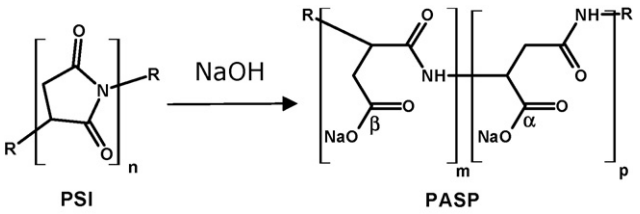

Scheme 1. Hydrolysis of polysuccinimide to sodium poly(aspartate). n, m, p denote the degree of polymerization ($n = m + p$). The monomer units distribute statistically in the PASP polymer.

shed light on the kinetics of these two physico-chemical reactions in different swelling agents.

2. Materials and methods

2.1. The synthesis of polysuccinimide (PSI)

PSI was synthesized by thermal polycondensation of aspartic acid (Reanal, Hungary) with phosphoric acid (Reanal), using a solvent mixture of mesitylene (Sigma) and sulfolane (Sigma) [12,13]. The average molecular mass of PSI chains was determined by static light scattering technique and was found to be 73 000.

2.2. Preparation of PSI based gels

In order to crosslink the precursor polymer chains, 0.97 g of PSI (0.01 mol succinimide monomer unit) was dissolved in 10 ml dimethylformamide (DMF; Reanal) and 0.088 g 1,4-diaminobutane (DAB; Sigma) was added under continuous stirring. The reactive mixture was poured into spherical glass moulds to yield spherical gel beads of 2–5 mm in diameter. The rate of monomer units and crosslinker molecules in the gel is 10, however our experiences have shown that only $25 \pm 5\%$ of the crosslinkers make connection between polymers. These results will be published in due course, together with equilibrium swelling measurements.

2.3. Preparation of poly(aspartic acid) (PASP) based gels

The transparent PSI gel beads obtained in the previous synthesis was transferred into 50 ml 0.1 M NaOH solution at room temperature for 3 h. The gels first became opaque due to the diffusion of water into the polymer network and then the turbidity changed slowly to transparent again starting from their surface. Upon alkaline hydrolysis, poly(aspartic acid) is formed, containing both α- and β-peptide bonds as depicted in Scheme 1. Polymer concentration in the gel beads at hydrolyzed form was 0.2 mol/dm^3.

2.4. Swelling kinetics

PASP and PSI gel beads (2–5 mm in diameter) were placed into pH 8 and pH 14 solutions under a Hund Wetzlar microscope equipped with a lamp of polarized light and a Sony CCD camera connected to a time laps video cassette recorder (Panasonic AG6720A). The applied solvents were of borate buffer with pH 8, $c = 0.1$ M concentration and $I = 0.25$ M ionic strength and NaOH solution $c = 1$ M concentration. After reaching the equilibrium size of the investigated systems, the video was stopped and the film was digitized by the PC program Doku 2.11.007 version 1.1a (Soft Imaging Systems GmBH). The size-evolution of the gel was finally assessed using Adobe Photoshop 7.0.

3. Theoretical background

The swelling kinetics of spherical gels was first quantitatively analyzed by Tanaka et al. [16,17]. The authors introduced a displacement vector $u(r,t)$ to represent the displacement of a point from its equilibrium state. This theory leads to the following prediction for spherical gels:

$$u(r, t) = \sum_n F_n(r) \exp\left(-\frac{t}{\tau_n}\right) \tag{1}$$

where F_n is a parameter and $\tau = a(\infty)^2/(D_c\alpha^2)$ is the relaxation time. D_c is the cooperative diffusion coefficient of solvent inside the gel, $a(\infty)$ is the equilibrium radius of the swollen gel and α is a constant. Translating this into measurable quantities:

$$\Delta a(t) = a(\infty) - a(t) = u_0 \sum_n B_n \exp\left(-\frac{t}{\tau_n}\right), \tag{2}$$

where u_0 is the displacement vector of the gel in the beginning of the swelling procedure, $u_0 = a(\infty) - a(0)$ and B_n is constant.

If t is comparable, or significantly longer than τ, Eq. (2) can be approximated with the first member of the series,

$$\ln\left(\frac{a(\infty) - a(t)}{a(\infty) - a(0)}\right) = \ln\ B_1 - \frac{t}{\tau_1} \tag{3}$$

Eq. (3) can be used to determine the relaxation time τ_1 as well as the parameter B_1. This latter is a complex function of R, which is the ratio of elastic shear modulus to the longitudinal modulus [16,17].

According to theory, R is independent of molecular details and is determined by the quality of solvent only. In theta solvent, the neutral gel is considered as a collection of phantom (Gaussian) chains and $R = 1/2$ is predicted, while for real (self avoiding) chains, $R = 1/3$ holds. Several works have provided experimental evidence for these predicted values [18,22].

Eq. (3) allows the determination of B_1 as the linear extrapolation of the logarithmic plot (intercept) and τ_1 from the slope of the dependence. Once the value of B_1 has been established, one can obtain the value of R. From the relaxation time (τ_1), it is possible to determine the cooperative diffusion coefficient D_c, as follows:

$$D_c = \frac{a(\infty)^2}{\tau_1 \alpha_1^2} \tag{4}$$

where $a(\infty)$ stands for the radius of the gel in the final equilibrium state and the $\alpha_1 = f(R)$ function is given in the literature [17].