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Synthesis and swelling properties of novel pH-sensitive poly(aspartic acid) gels

Tamás Gyenes, Viktória Torma, Benjámin Gyarmati, Miklós Zrínyi *

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

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Abstract

Chemically cross-linked poly(aspartic acid) (PASP) gels were prepared by the hydrolysis of poly(succinimide) (PSI). The latter was prepared by thermal polycondensation of aspartic acid. The PSI chains were cross-linked by natural amines and amino acid derivatives such as putrescin, spermine, spermidine, lysine and cystamine to obtain biodegradable, biocompatible, amino acid-based hydrogels. The volume of the synthesized unhydrolyzed PSI gels changes abruptly at a well-defined pH that results in ring opening, while the hydrolyzed gels show a volume phase transition around the p*K* values of PASP. The unidirectional stress–strain behavior of the gels as well as the dependence of equilibrium swelling degree on the pH was carefully studied and the most important network parameters were determined by a modified version of the Brannon–Peppas–Peppas theory.

Keywords: Poly(aspartic acid); Poly(succinimide); Polymer gel; pH sensitivity; Swelling

1. Introduction

Novel polymer gels that are responsive to external stimuli have been developed in the past decade [1,2]. The stimuli that have been investigated to induce volume change are diverse, and include temperature [3–5], pH [5–7], solvent and ionic composition [8,9], electric field [10,11], light intensity [12] and the introduction of specific molecules [13]. The discovery of a discontinuous volume phase transition in gels, which is often called collapse transition, has rendered such soft materials technologically useful [14]. The applications of these gels can be utilized in controlled-release delivery and separation systems [15,16].

Polymer materials capable of releasing physically entrapped drugs and chemicals on demand by well-defined kinetics have been receiving increasing attention recently. Implementation of hydrogels as novel controlled-release matrices is based on the following main characteristics [13,17,18]:

- Drug molecules can be physically or covalently incorporated into the networks.
- Material properties are highly tunable by modifying either the cross-link density or the environmental conditions.
- Polymer networks can be designed to change swelling degree, elasticity, solubility and transport properties in response to externally applied triggers, such as temperature, ionic strength, pH, solvent polarity, light, electric and magnetic fields.
- The permeability of solutes through gels depends on the chemical structure and the swelling degree of the swollen network.

Smart hydrogels showing strong and abrupt response to small changes in environmental conditions have been the subject of much recent interest. The most frequently studied gels having environmental sensitivity are either

* Corresponding author. Tel.: +36 14633229.
E-mail address: zrinyi@mail.bme.hu (M. Zrínyi).

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temperature- [3,4] or pH-sensitive [5,6] gels. The temperature-sensitive gels (showing collapse transition) are usually characterized by a lower critical temperature (LCST) of the backbone polymer or copolymer comprising the gel [19]. For instance poly(*N*-isopropylacrylamide) is a representative temperature-sensitive polymer [3]. The pH sensitivity requires addition of ionic monomers to the hydrogel. For such polyelectrolyte gels, as the pH of local environment changes from acidic to alkaline, the gel undergoes a volume change. Depending on the chemical composition, the volume change can be either continuous or abrupt. In order to develop pH-sensitive, targetable drug delivery matrices, polyelectrolyte gels with abrupt volume change are required. Besides this stimulus-response attribute, the biocompatibility and biodegradability of the drug carrier is also important. Much effort has been directed recently towards designing biocompatible and biodegradable polymers for drug carriers [20]. Protein-based polymers that have desirable chemical, mechanical and biological properties have recently emerged as a promising new class of materials [21]. As opposed to many synthetic materials, for poly(amino acid)-based materials the degradation products are small-molecules nutrients, which are excreted or utilized by physiological processes in the body. Besides the biocompatibility and biodegradability, the main reason for the use of poly(amino acid)-based biomaterials is their virtually unlimited structural diversity. In poly(amino acid) chains the amino acids are joined by amide linkages. These peptide bonds are stable, and prolonged exposure to a strong acid or base at elevated temperatures is required to hydrolyze these bonds nonenzymatically. It is the nature of the side chains that provides the great structural diversity. Side chains of 20 different types of amino acids can be classified as nonpolar-, uncharged polar-, acidic- and basic side chains. Non-polar side chains promote hydrophobic interactions, uncharged polar side chains are responsible for hydrophilic interactions, while the influence of acidic- and basic side chains essentially differ in charged, hydrophilic (protonated bases or deprotonated acids) and in uncharged, hydrophobic (deprotonated bases or protonated acids) form. A well-defined balance between hydrophobic and hydrophilic interactions is the necessary condition of abrupt volume change of polyelectrolyte gels. Poly(amino acids) with free carboxylic acid groups such as poly(aspartic acid) (PASP) or poly(glutamic acid) are good candidates for biodegradable, pH-responsive polymer gels.

Intensive exploration of poly(amino acids) started half century ago. Much of the initial work on poly(amino acids) was reviewed by Katchalski and Sela [22]. Significant advances in the field of preparation have been made by Tirrell et al. [23] and Urry [24]. Today the most widely investigated medical applications are in the area of drug delivery. Numerous publications have described the use of poly(amino acids) as water-soluble macromolecular carriers for a variety of pharmacologically active agents. The search for controlled-release matrices has been essentially limited to a very narrow subset of all available poly(amino acids). Esterified poly(glutamic acid), copolymers of poly (γ-benzyl-L-glutamate), poly(*N*-dihydroxyethylaminopropyl-L-glutamine) [25] and poly(lysine) [26] have been suggested as materials for drug delivery. The attachment of amino-group-containing drug molecules to the carboxylic acid side group of poly(glutamic acid) or PASP chains is also a current research direction [27].

Several research papers have been published about the synthesis of PASP, but only a little attention has been devoted to the network formation by chemical cross-links as well as to the swelling properties of PASP gels.

In this paper we aim to report the synthesis of novel pH-responsive PASP gels and material properties that are important for developing new types of controlled-release matrices. Our main research aim was to combine the desirable material properties of PASP, with the responsive properties of hydrogel to develop a novel matrix for controlled drug delivery.

The main purpose of the present work was to prepare chemically cross-linked PASP gels by using natural polyamines (putrescin, spermidine and spermine) as well as amino acid derivatives (lysine methyl ester or cystamine) as cross-linking agents. The dependence of equilibrium swelling degree on the pH was carefully studied and the most important network parameters were determined by modified version of the Brannon–Peppas–Peppas theory [28].

This paper is organized as follows. First the preparation procedure is described. This includes the synthesis of linear poly(succinimide) (PSI) chains, the cross-linking process as well as the hydrolysis of PSI networks to PASP gels. The synthesis of both PSI and PASP gels is followed by the experimental investigation of the gels. The unidirectional stress–strain behavior of PSI-based gels as well as dependence of equilibrium swelling degree on the pH in the case of PASP-based gels is discussed. The measured equilibrium swelling degree data are then interpreted on the basis of a modified Brannon–Peppas–Peppas theory.

2. Materials and methods

2.1. Materials

L-Aspartic acid (puriss, 99.0%), phosphoric acid (a.r., 85%), methanol (p.a. 99.8%), citric acid monohydrate (a.r., 99.5%) and sodium chloride (p.a., 99.8%) were obtained from Reanal (Hungary). Mesitylene (Fluka, purum, 98%), sulfolane (Aldrich, 99%), dimethyl sulfoxide (DMSO, Fluka, purum, 99%), dimethylformamide (DMF, Fluka, purum, 99%), diaminobutane (DAB, Fluka, puriss, 98%), dibutylamine (DBA, Riedel-de Haën, 99%), cystamine dihydrochloride ($Cys_2 \cdot 2HCl$, Fluka, purum, 98%) from Sigma–Aldrich were used. Lysine methyl ester hydrochloride ($HLysOMe \cdot 2HCl$, 99%) were purchased from Bachem (Germany). All reagents and solvents were used without further purification.